Current Management of Type 2 Diabetes

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Primary Care Internal Medicine:
Principles & Practice

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Prevalence of Diabetes in the U.S.

CDC 2011

Prevalence of all diabetes	26	million
Type 1	1+	million (0.4%)
Type 2	24.5	million (8.3%)
Diagnosed	18	million (7.0%)
Undiagnosed	7	million (2.0%)

1,900,000 cases per year

GDM	100,000	(3-5% of all pregnancies)
Prediabetes	72	million (20%)

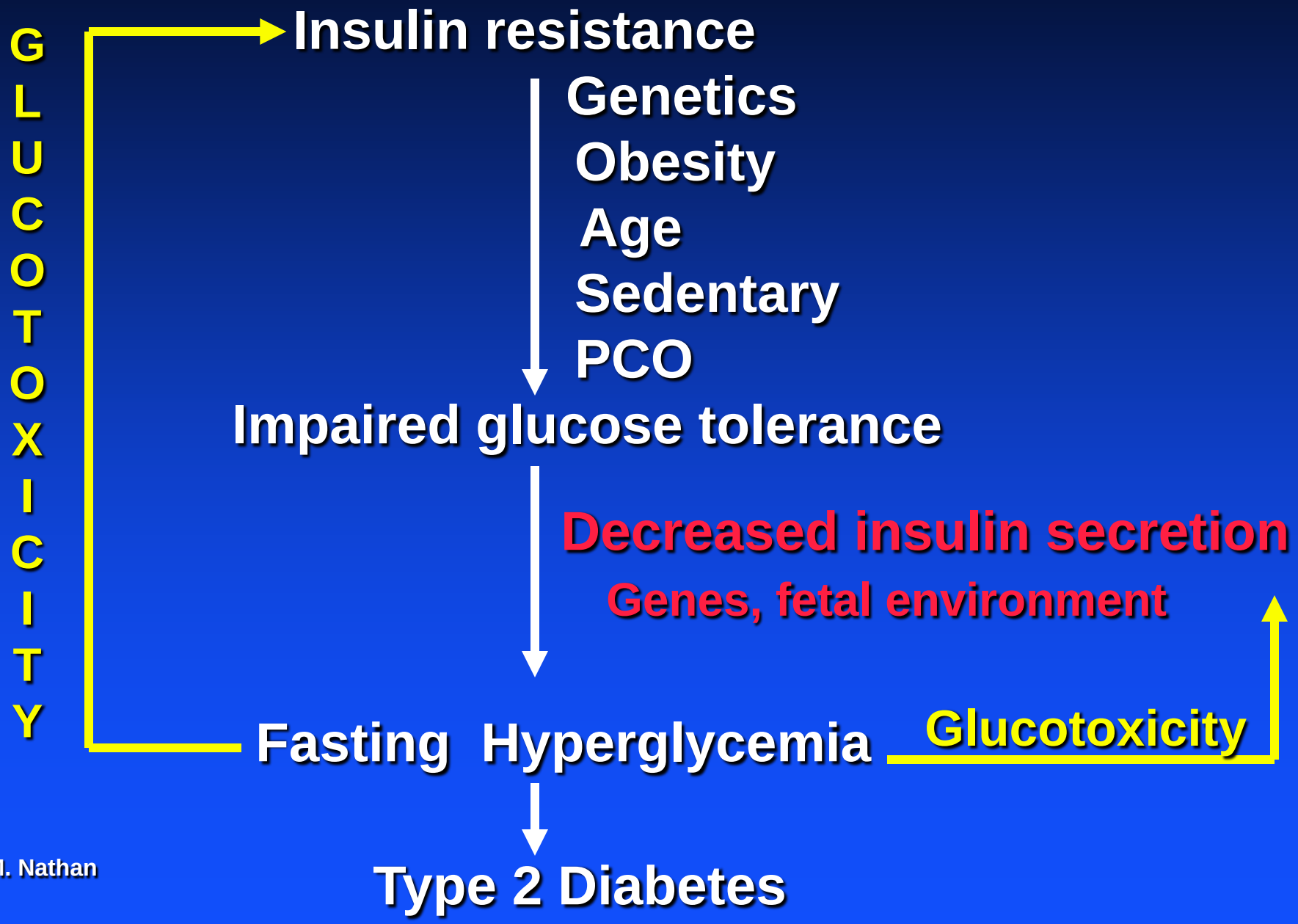
HEALTH CARE BURDEN ASSOCIATED WITH DIABETES IN U.S.

- Most common cause of ESRD in adults
- Most common cause of blindness
- Most common cause of amputations
- 2-5 fold increased risk for CVD

In the aggregate, costs attributed to diabetes total more than $194 billion dollars per year.*

*ADA, 2011

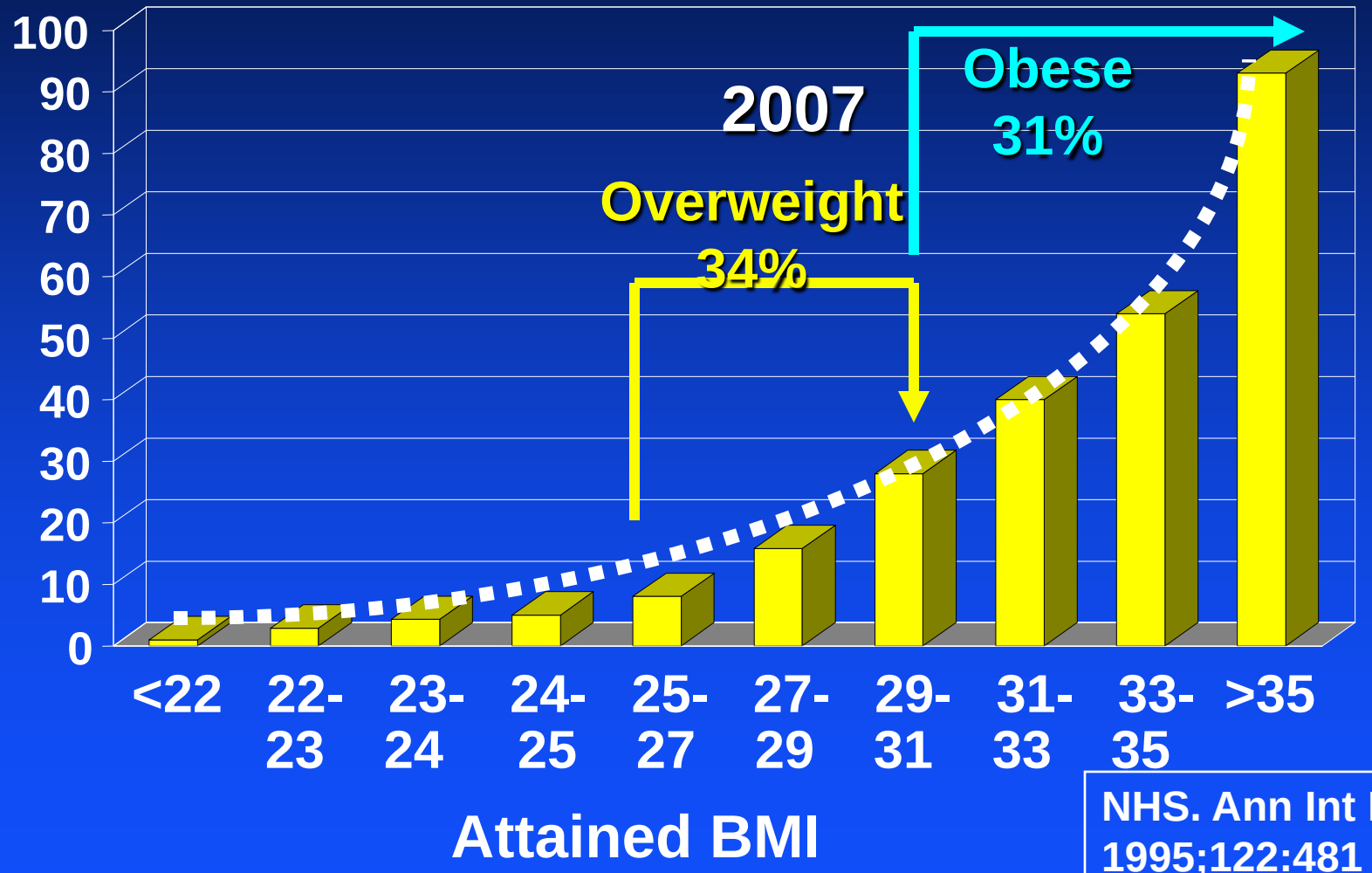
Pathophysiology of Type 2 Diabetes



Risk for Development of Type 2 Diabetes

Effect of BMI in Women

Age-adjusted RR(%) of Developing DM over 14 yr In women aged 30-55 in 1976

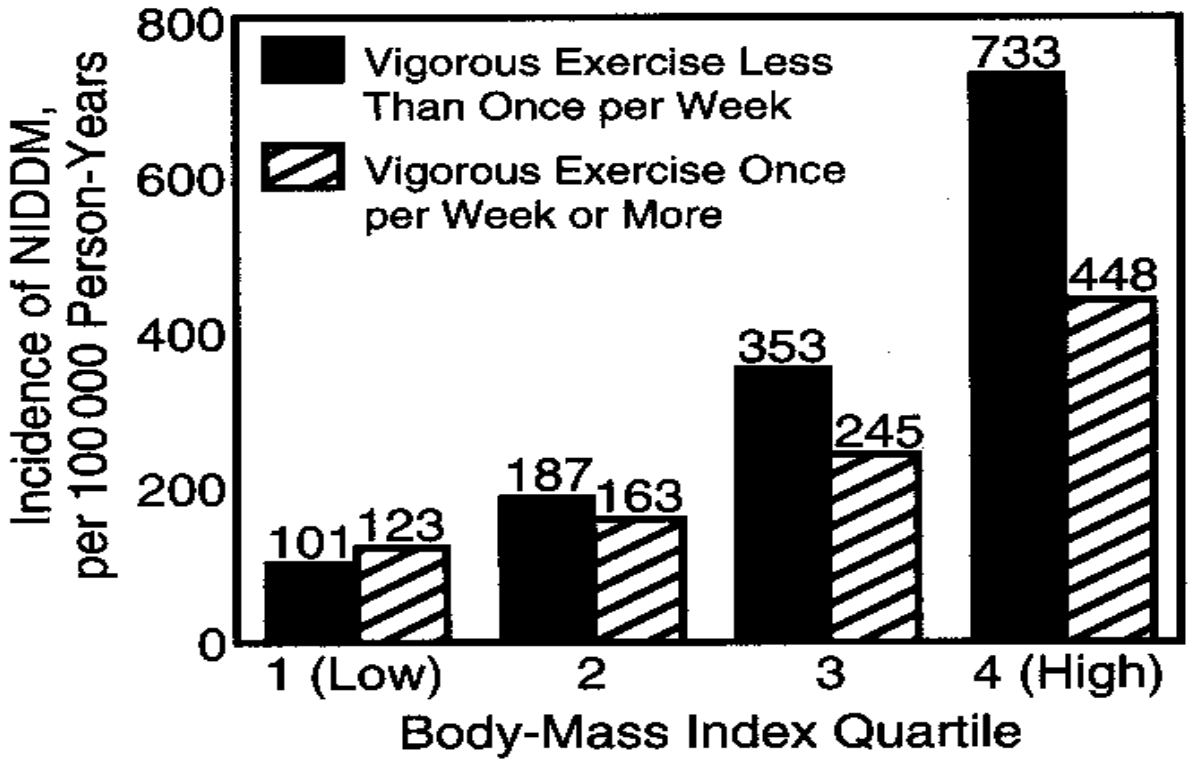


NHS. Ann Int Med 1995;122:481

Relationship between Exercise and Incidence of Diabetes

Physicians' Health Study

21,000 physicians followed for a mean of 5 years

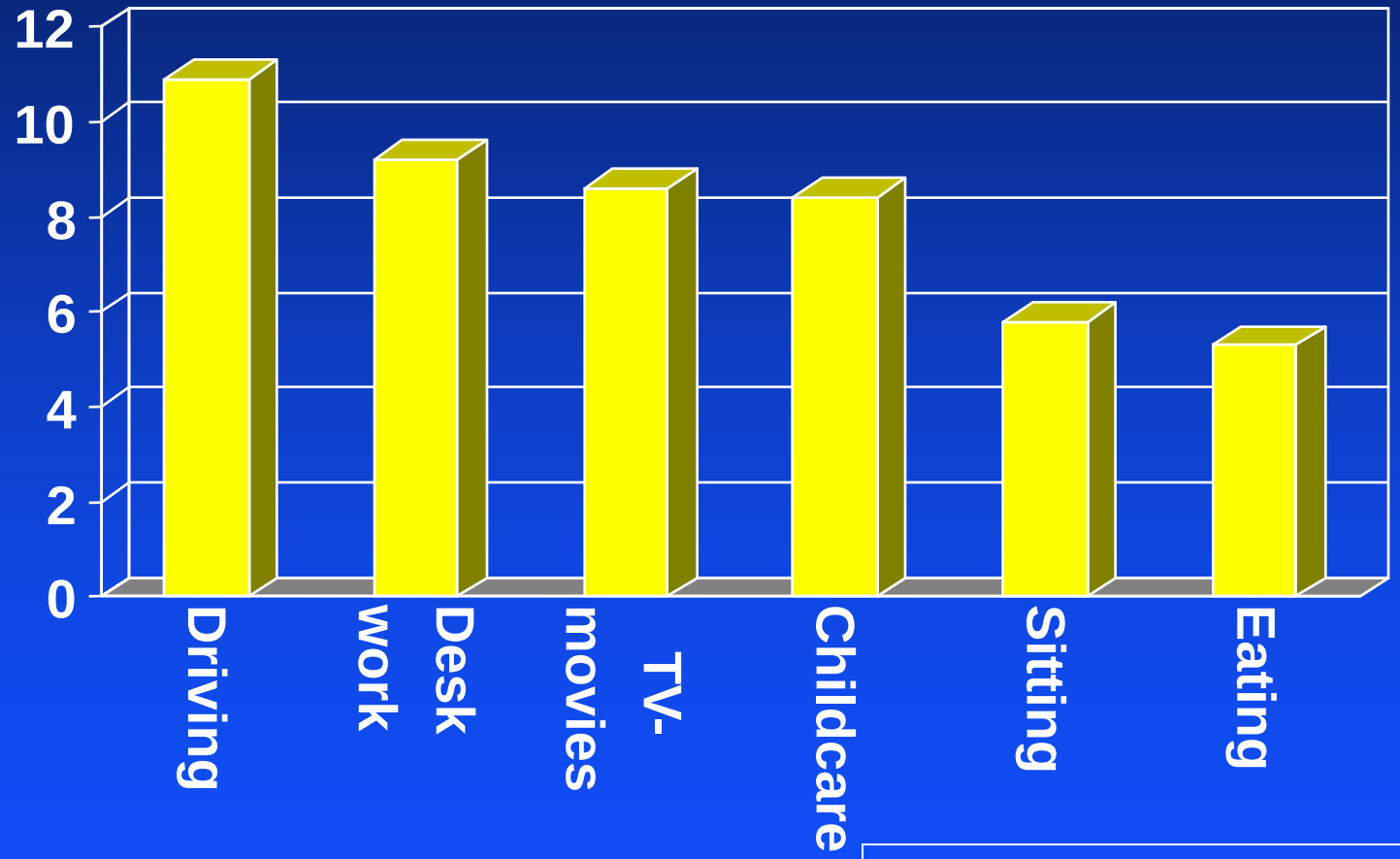


Manson, Nathan et al. JAMA 1992; 268:63

Physical Activity in US

National Human Activity Pattern Survey

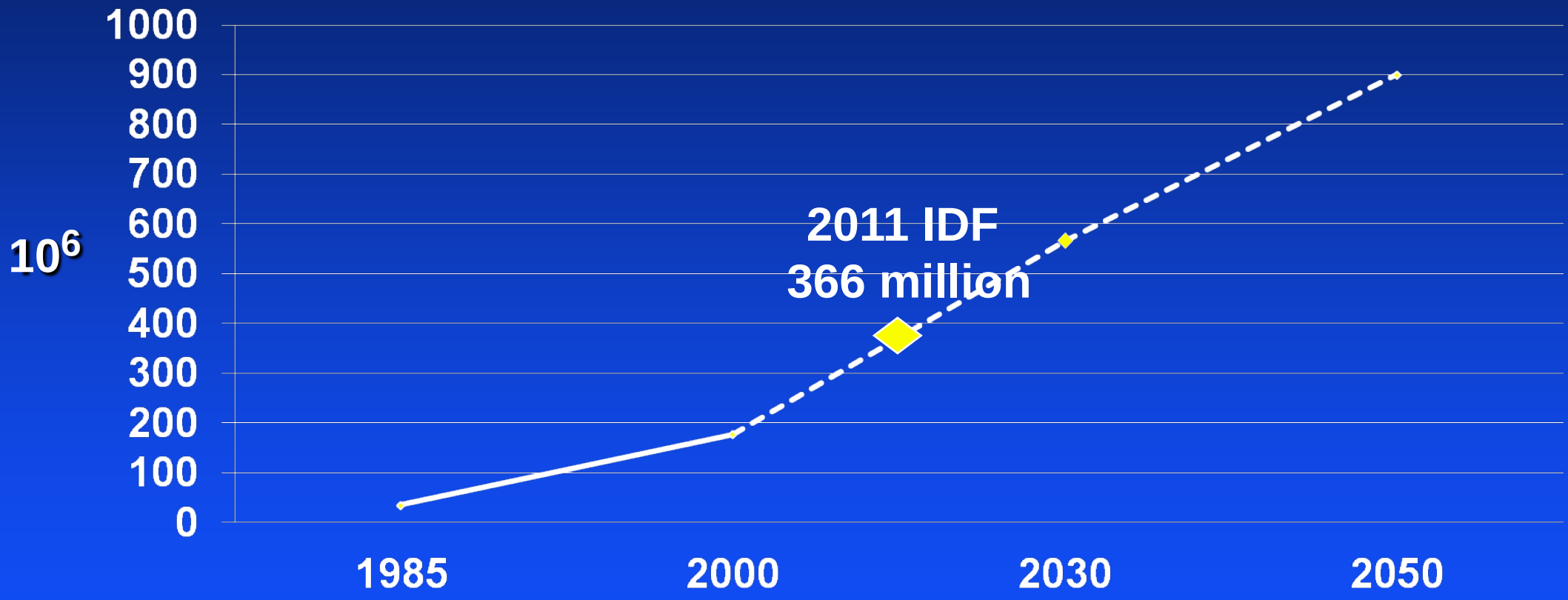
% of total energy expenditure not including sleep



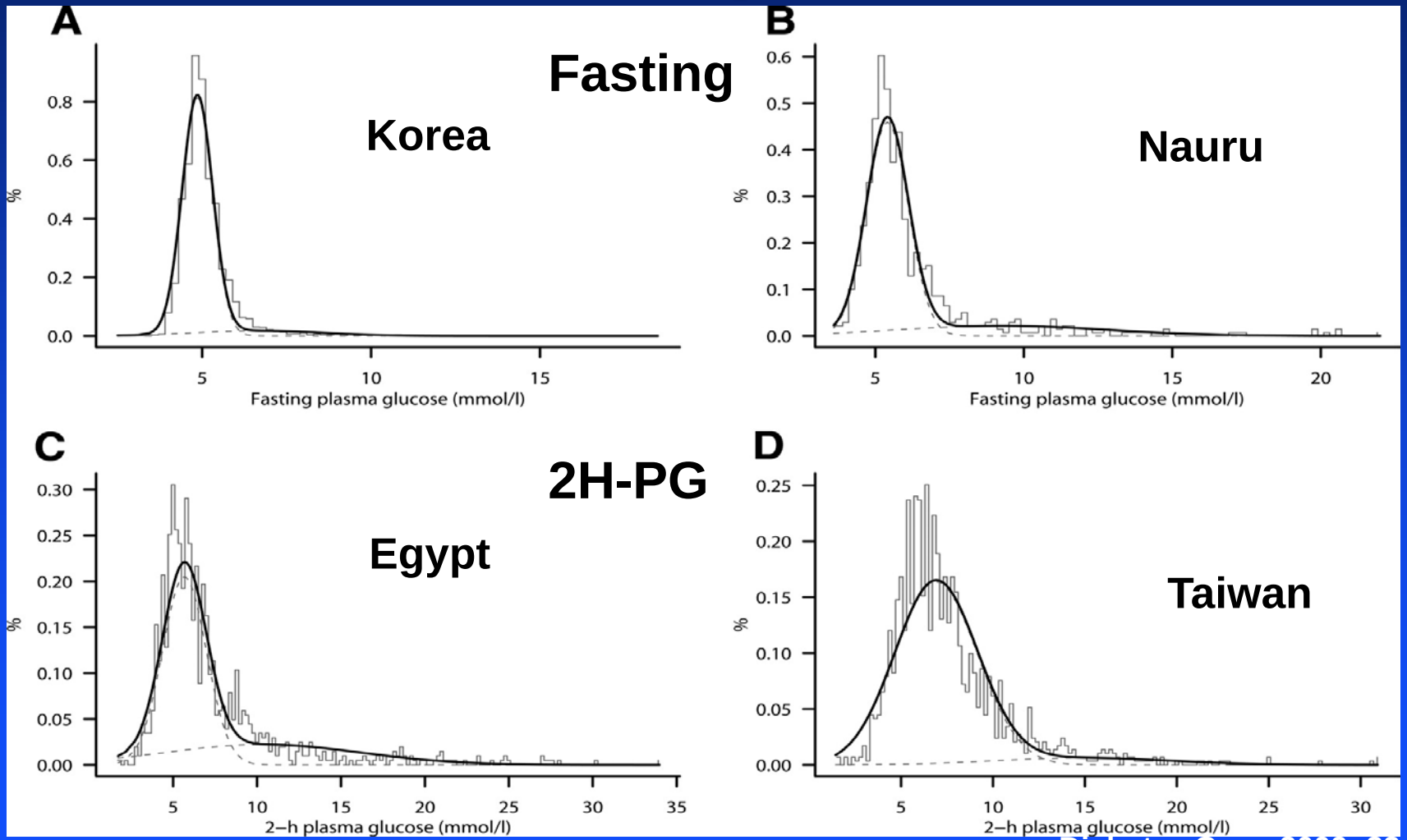
7515 adults. 24 hr recall of all activities 1992-94.

Int J Behav Nutr and Phys Activity 2004; 1:4

Diabetes Pandemic



Diagnosis of Diabetes: Distribution of FPG and 2hrPG in Four Populations



Diabetes Care, 2009: 32,

History of Diagnostic Methods

Paradigm Shift in 1997:
Association with Long-term Complications

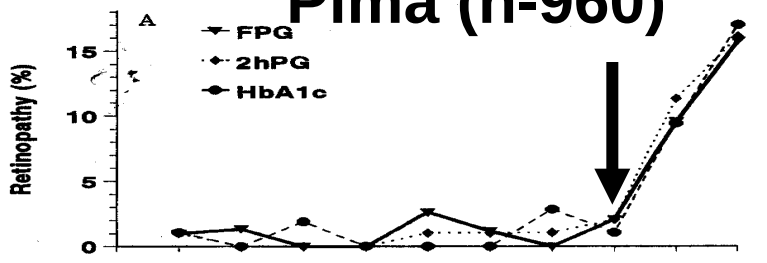
- **Expert Committee 1997, WHO consultation 1999**
  - Based diagnostic glucose levels on association with prevalence of retinopathy in 3 populations: Egyptian, Pima, NHANES
  - Measured retinopathy with photography or dilated fundoscopy
  - Glycemia measured as FPG, 2HPG and A1C

1997 ADA Expert Committee

Association of Glycemia with Complications

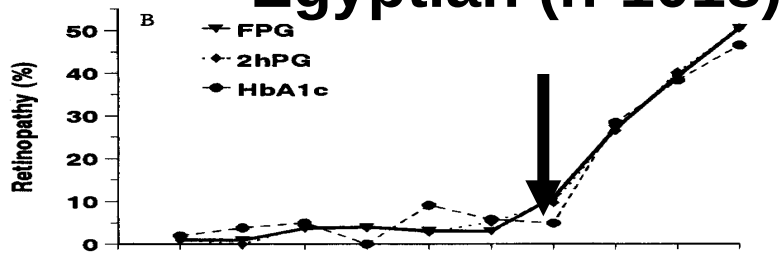
Retinopathy

Pima (n-960)



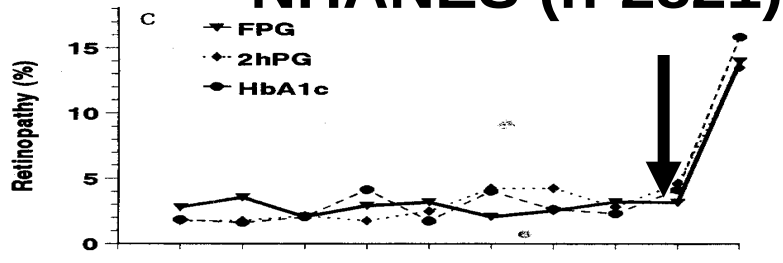
FPG (mg/dl)	70-	89-	93-	97-	100-	105-	109-	116-	136-	226-
2hPG (mg/dl)	38-	94-	106-	116-	126-	138-	156-	185-	244-	364-
HbA1c (%)	3.4-	4.8-	5.0-	5.2-	5.3-	5.5-	5.7-	6.0-	6.7-	9.5-

Egyptian (n-1018)



FPG (mg/dl)	57-	79-	84-	89-	93-	99-	108-	130-	178-	258-
2hPG (mg/dl)	39-	80-	90-	99-	110-	125-	155-	218-	304-	386-
HbA1c (%)	2.2-	4.7-	4.9-	5.1-	5.4-	5.6-	6.0-	6.9-	8.5-	10.3-

NHANES (n-2821)



FPG (mg/dl)	42-	87-	90-	93-	96-	98-	101-	104-	109-	120-
2hPG (mg/dl)	34-	75-	86-	94-	102-	112-	120-	133-	154-	195-
HbA1c (%)	3.3-	4.9-	5.1-	5.2-	5.4-	5.5-	5.6-	5.7-	5.9-	6.2-

Cross-sectional

1997 ADA
Expert Committee

Expert Committee on Diagnosis of Diabetes

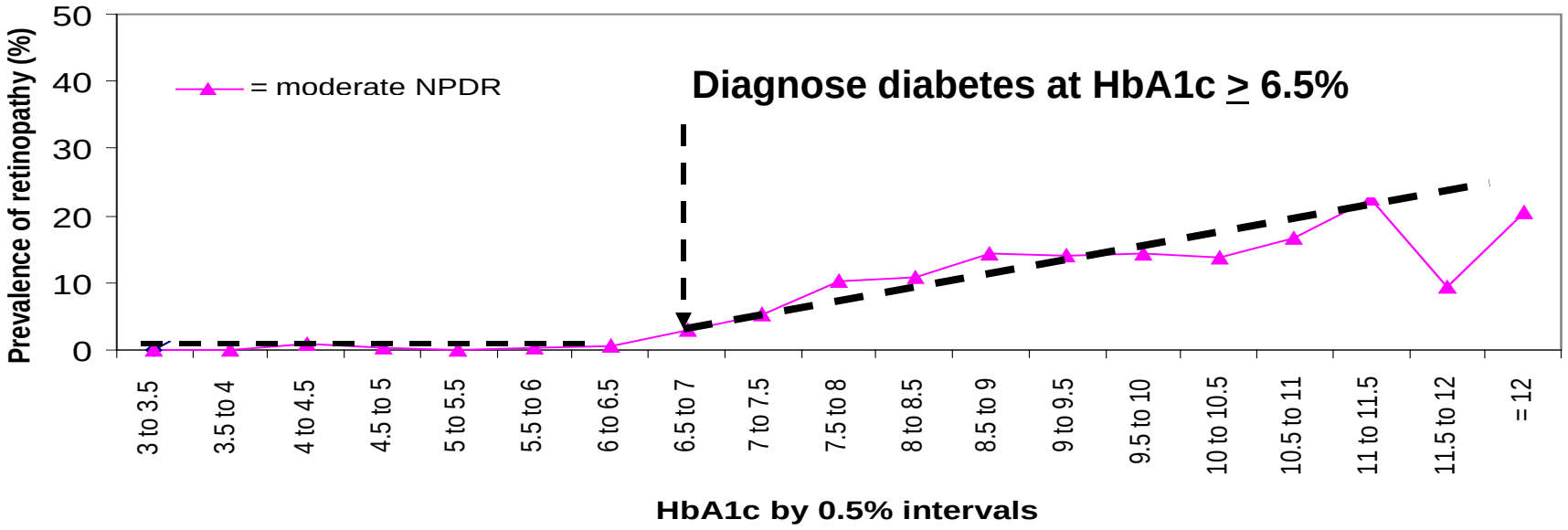
Technical Attributes of A1C vs FPG

	A1C	FPG
Pre-analytic		
Stability at 37° C	+	-
Stability over time	+	-
Analytic variance	+	+
Biological variance		
Intra-individual	Low	Higher
Inter-individual	Low	Higher
Clinical	No timing No preparation Unaffected by acute stress	Timed ≥ 8 hr fast Affected by everything

Expert Committee

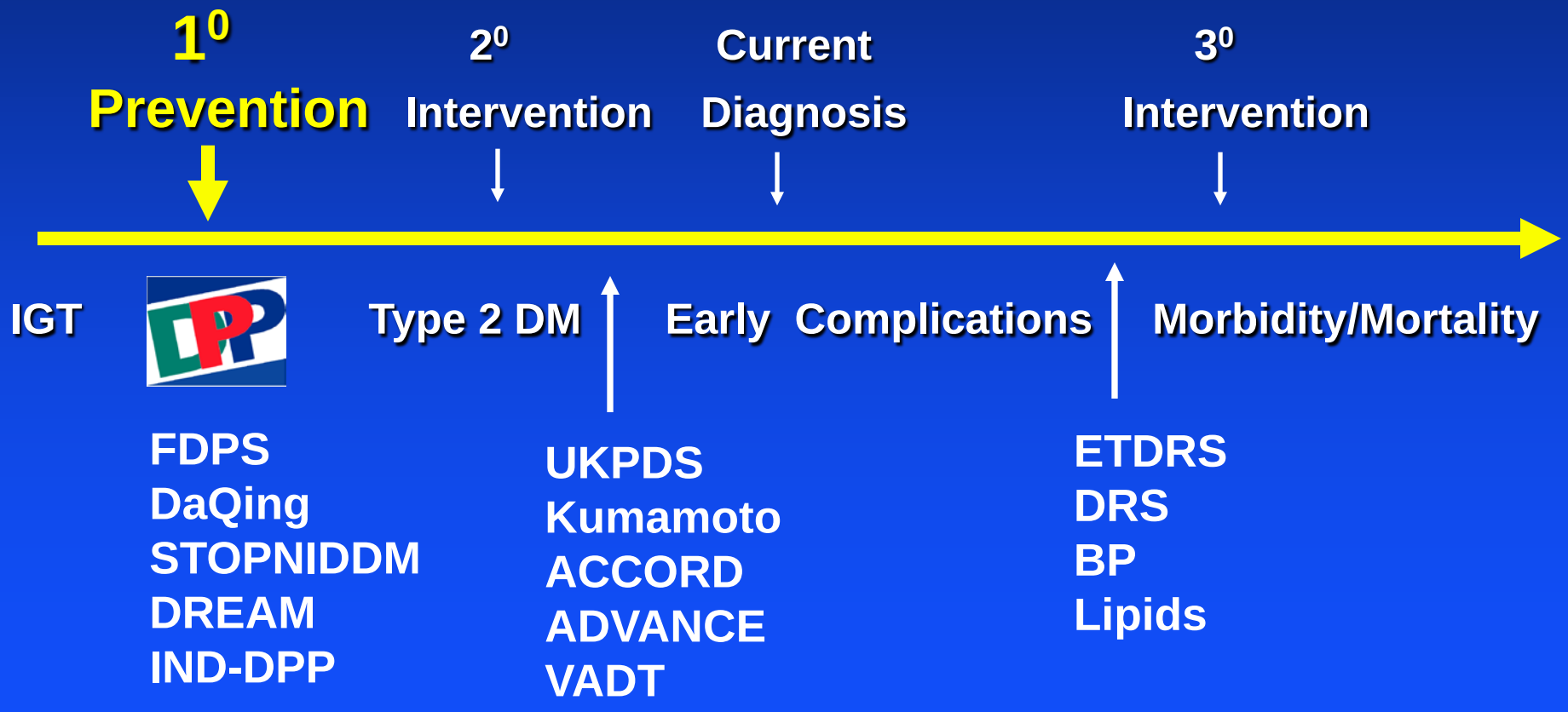
DETECT-2

~29,000 persons from 13 different population-based cohorts (Asia, Africa, Europe, NA) with HbA1c measurement, fundus photography and standardized measurements

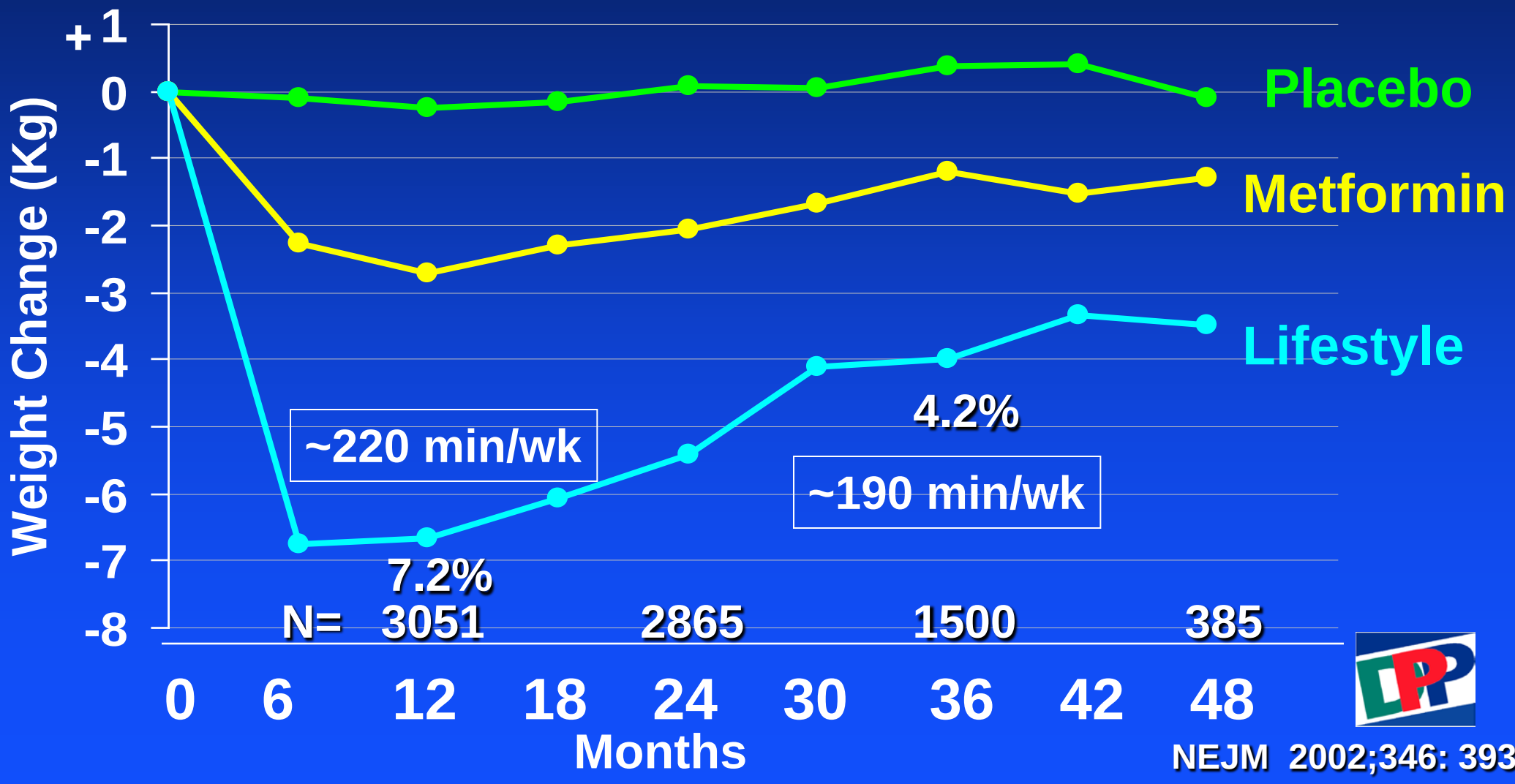


Virtually no moderate retinopathy below an A1c of 6.5%

Response to an Epidemic



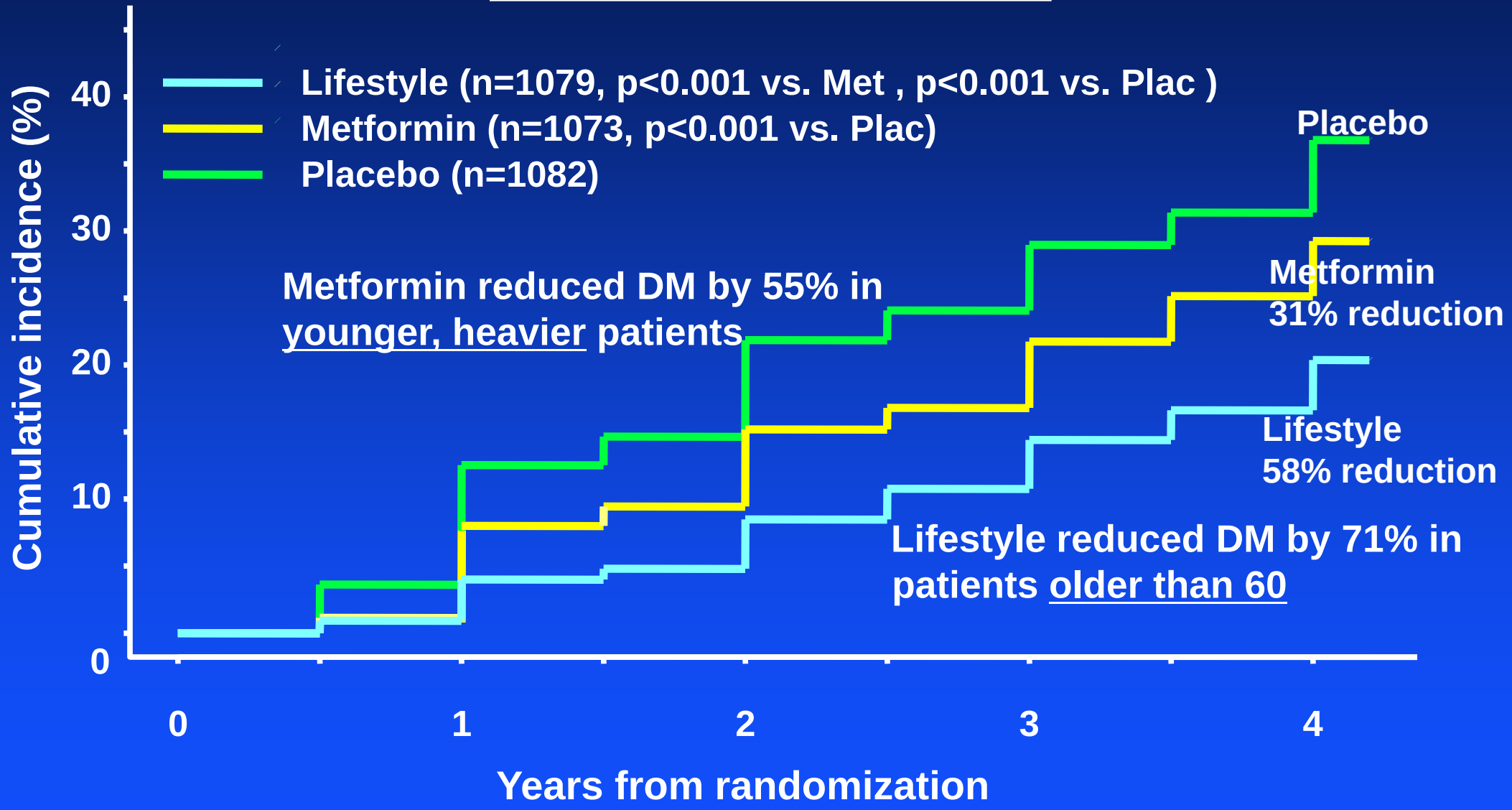
Mean Weight Change from Baseline



NEJM 2002;346: 393

Percent developing diabetes

All participants-2.8 years



NEJM 2002;346: 393

Long-term Diabetes Prevention

	After 2.8 years of DPP	After 10 years DPP/DPPOS
ILS	58%	34%
Metformin	31%	19%

Other Benefits over Time with ILS
(compared with placebo)

- Lower HbA1c but less frequent use of meds
- Lower BP and lipid levels with less frequent meds

Lancet 2009;374:1677

DPPOS OUTCOMES STUDY

Implementation

Cost-Effectiveness: 10-Year Within Trial DPP

Cost of prevention is greater for lifestyle ($4500 in 10 years), than for metformin ($2400) of for placebo (~$700)

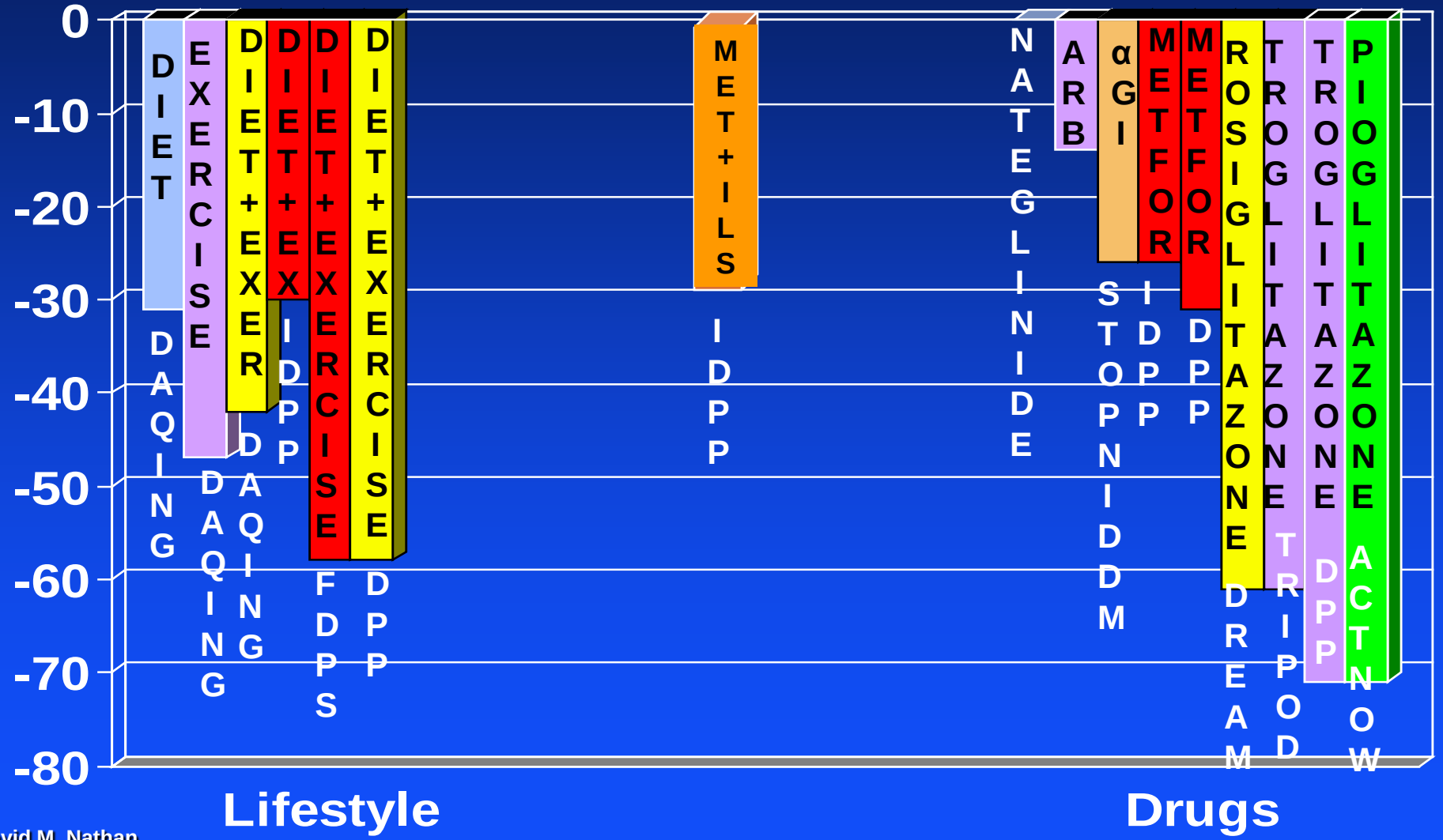
However, cost of overall medical care is much more with placebo group incurring a cost of $27,468, metformin $25,615 and lifestyle $24,463

Considering costs of care and prevention, in addition to health benefits metformin saves costs and lifestyle costs ~$800 compared with placebo

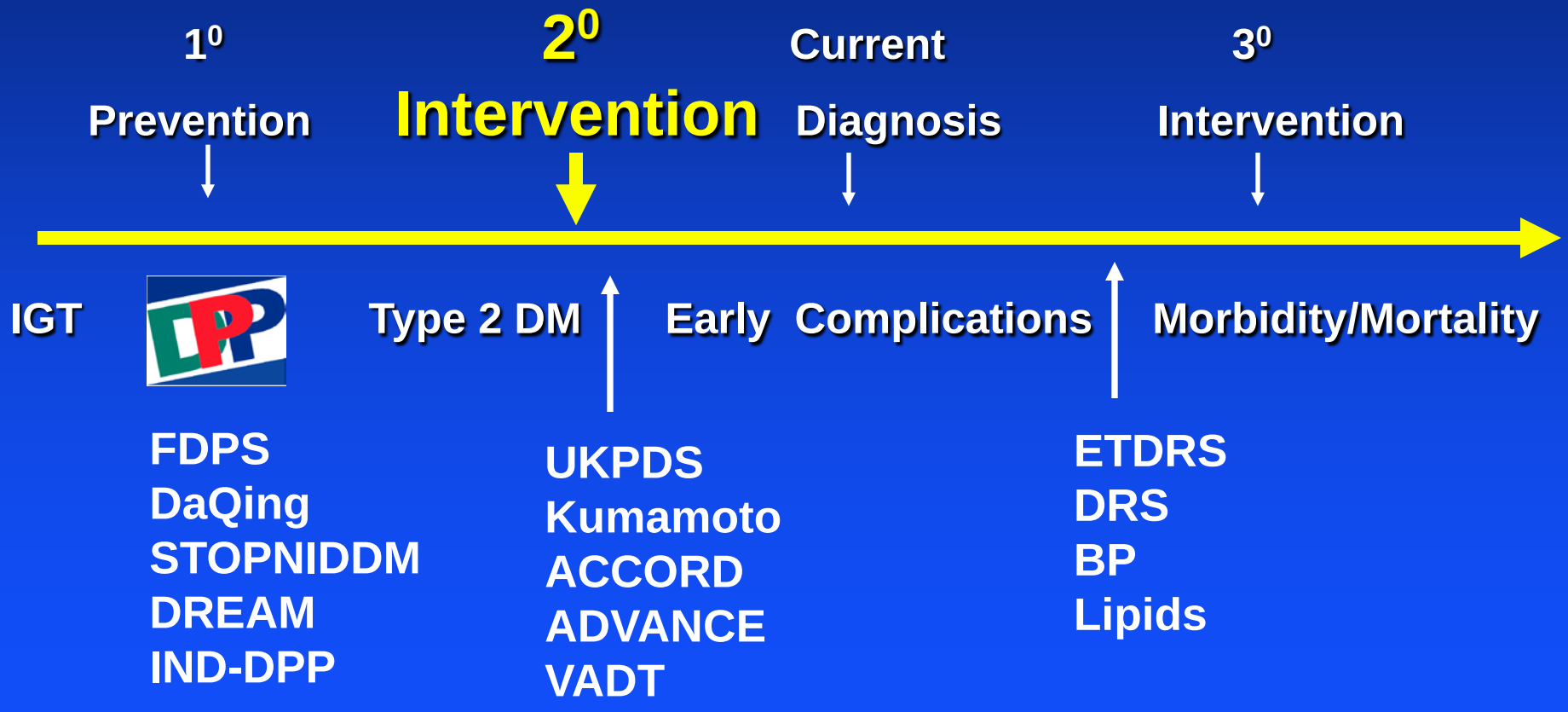
Diabetes Care 2012;35:723-30

Primary Prevention Trials

Reduction in Incidence Compared with Control

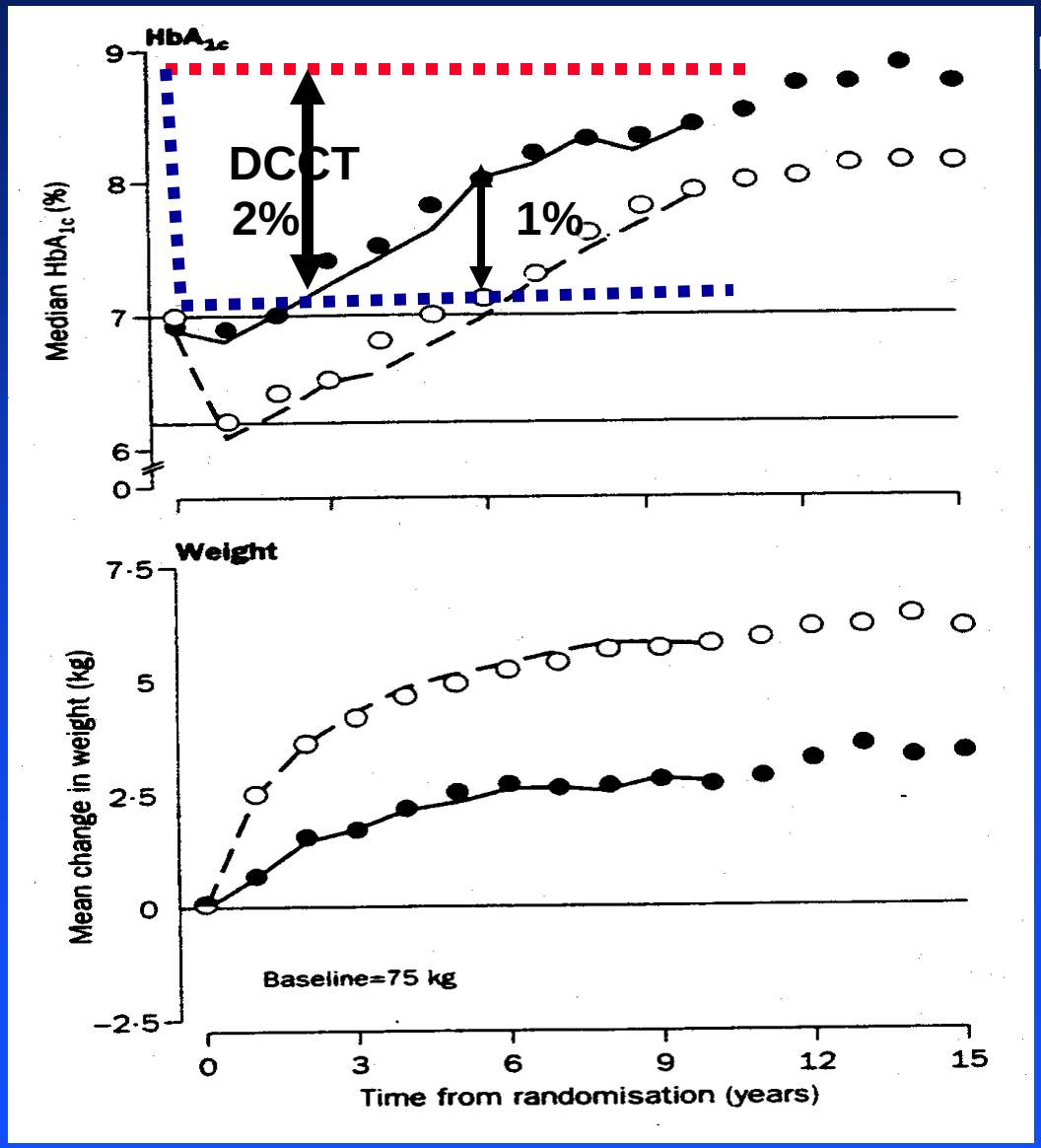


Response to an Epidemic



UKPDS Results: Establishing Goals

Obese and non-obese treated with conventional vs insulin/sulphonylureas



Mean 7.9%

Mean 7.0%

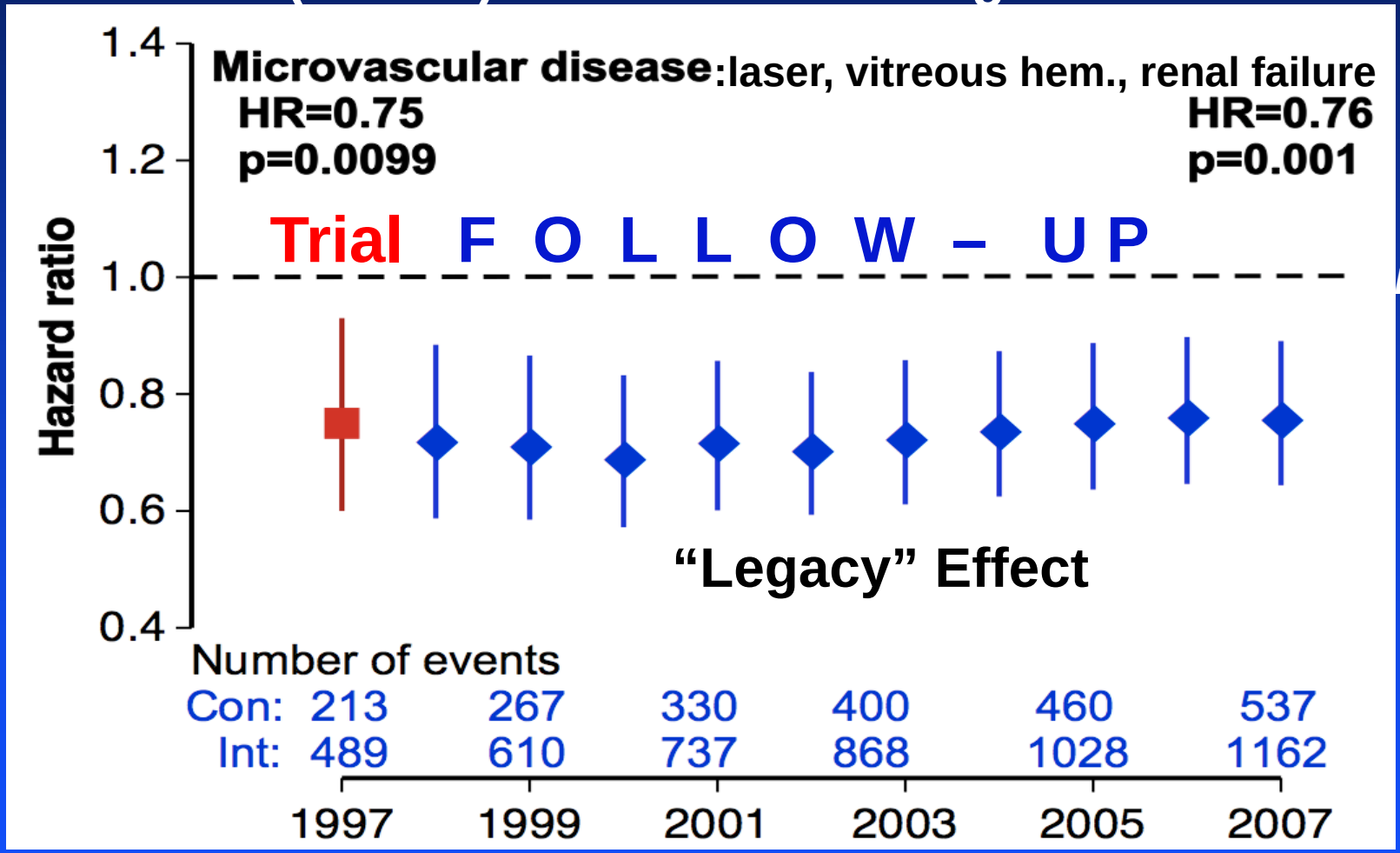
The worsening HbA1c over time in type 2 diabetes, despite the addition of more medications, was due, in large part to progressive beta-cell failure

UKPDS
Lancet
1998;352; 837.

Microvascular Disease Hazard Ratio

UKPDS

Intensive (SU/Ins) *vs.* Conventional glucose control



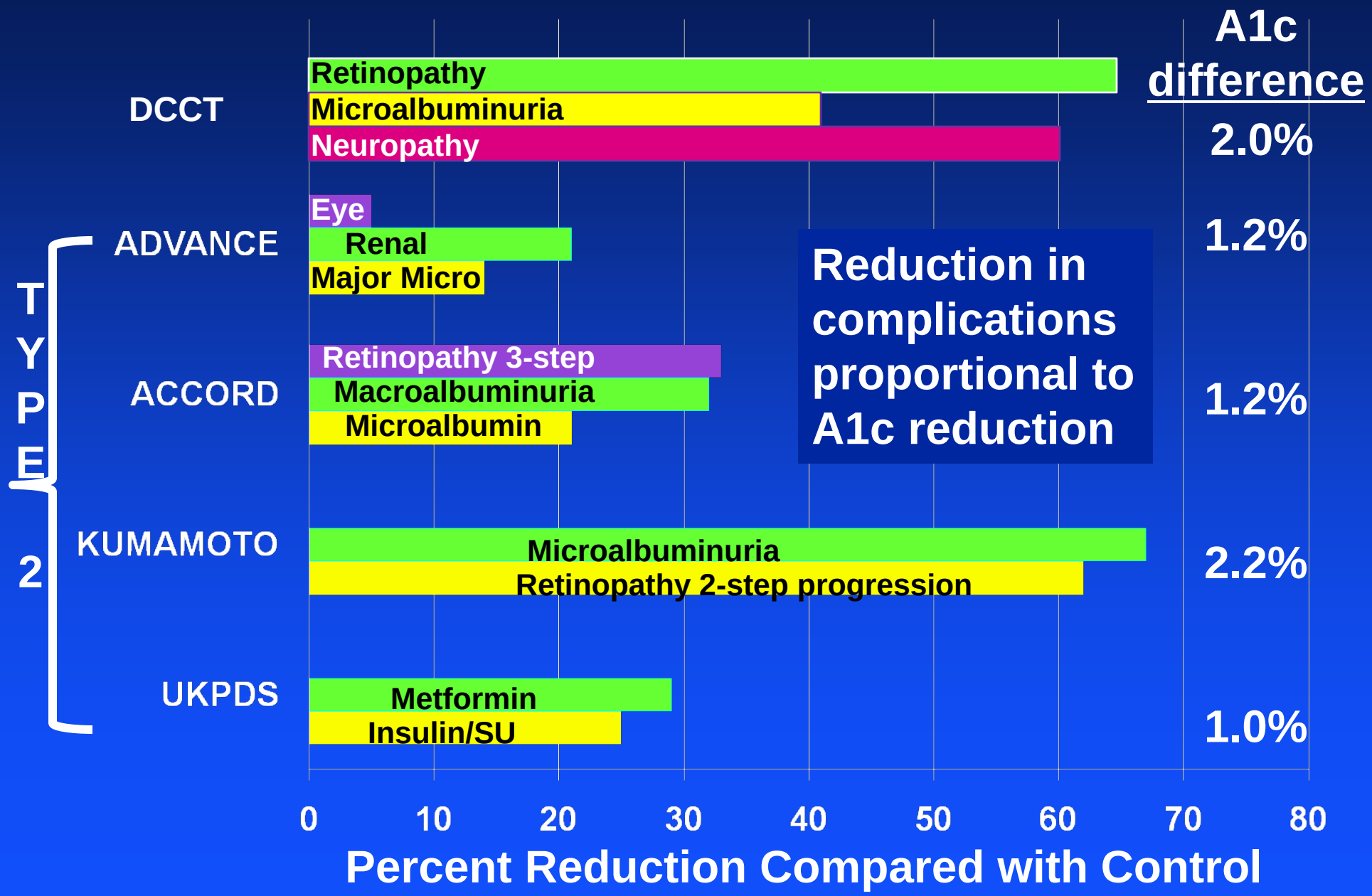
NEJM 2008; 359:

Control and Complications

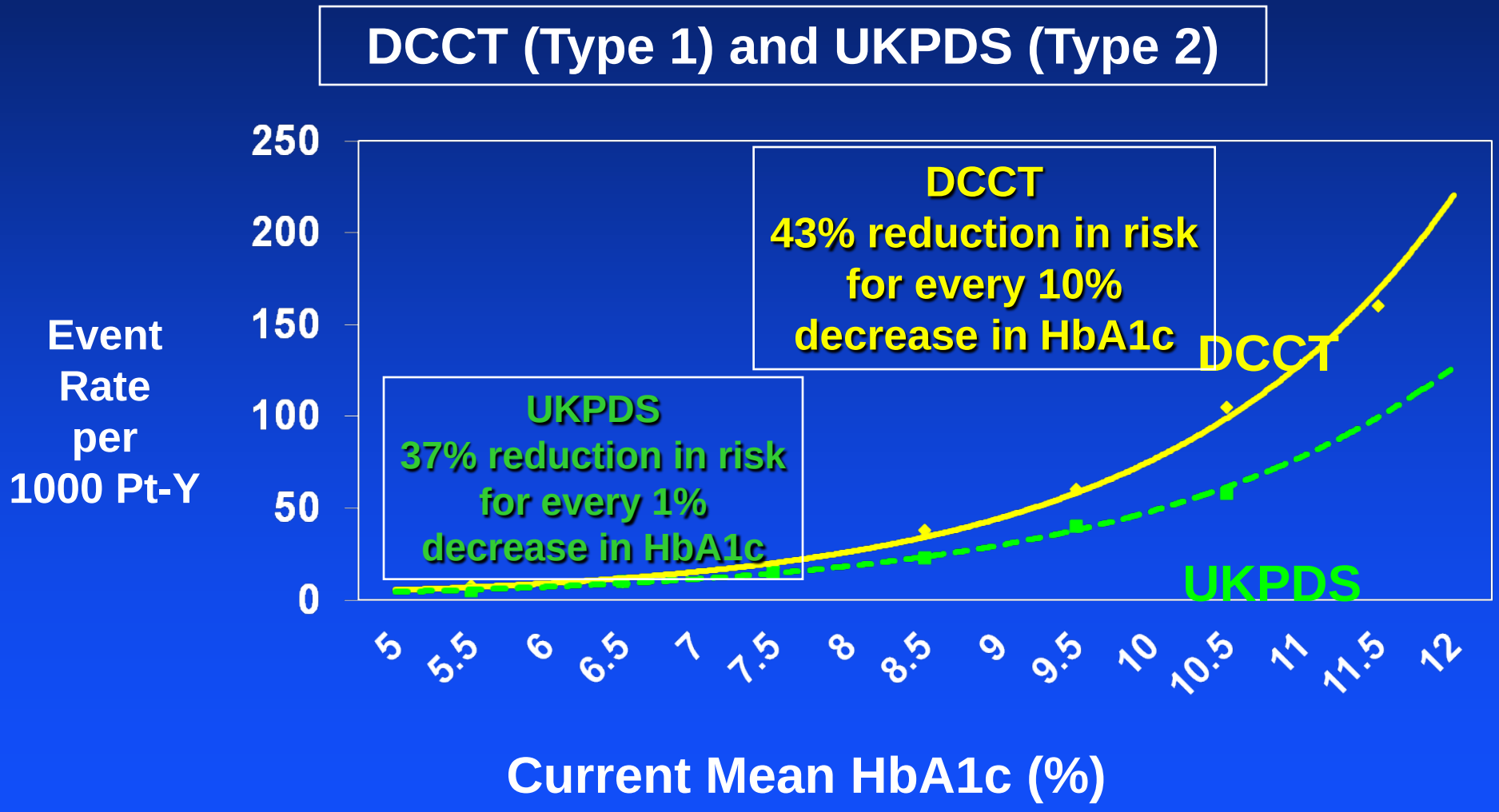
Microvascular

Study	Number	Duration DM (Y)	Duration Study (Y)	A1c (%)	Outcomes
UKPDS Metformin	3,867 753	<1 <1	11.1 10.7	7.9 vs 7.0 8.0 vs 7.4	Advanced eye/kidney
Kumamoto	110	8	8	9.4 vs 7.2	Eye/kidney/nerve
ACCORD ACCORD Eye	10,251 2,856	10	5 4	7.5 vs 6.4 7.5 vs 6.4	Advanced eye and /kidney 3-step change or PDR req. laser
ADVANCE	11,140	8	5	7.3 vs 6.3	Macroalbuminuria
VADT	1,791	11.5	5.6	8.4 vs 6.9	Eye (progression, PDR or ME), Renal (micro to macro, doubling of SeCr), clinical neuropathy

Microvascular Complications



Relationship between Glycemia and Complications



Current Treatment Goals

	HbA1c	Glucose (mg/dl) Pre-	Post-prandial
• ADA	< 7.0	70-120	< 180
• AACE	< 6.5	≤ 110	< 140
• IDF-Europe	< 6.5	< 110	≤ 135

Why Not Lower?

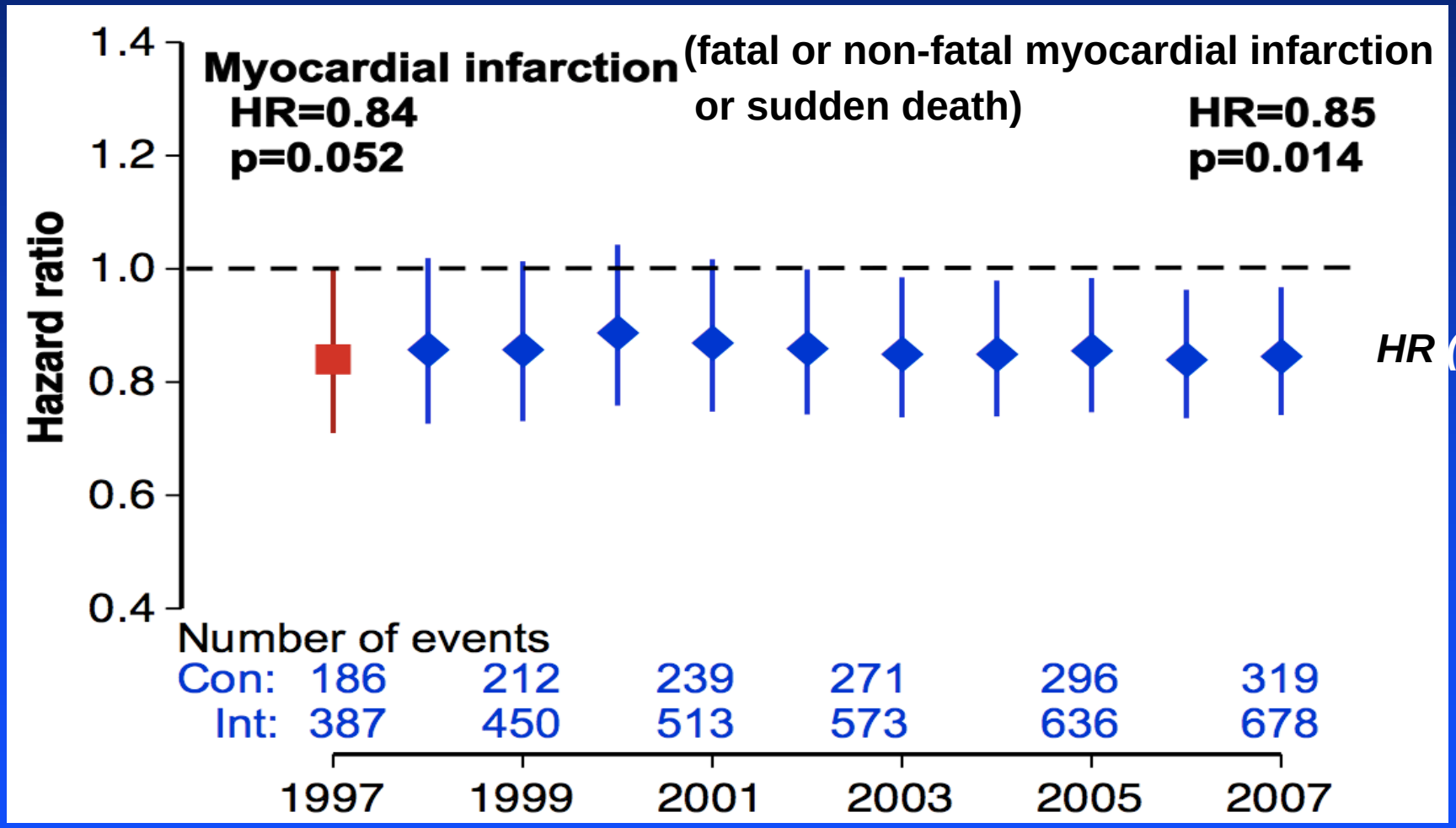
- Limited data in HbA1c range < 6.5%, until recently
- Not clear if the increased expense, effort, and risk for hypoglycemia is merited by added benefit
- No data to support benefit of very tight control on CVD
  - ACCORD, ADVANCE, VADT
  - 30-year UKPDS follow-up shows benefit of 7.0 v 7.9%
- ACCORD suggests possible harm

A1c <7% is an appropriate goal for drug treatment for now

Myocardial Infarction Hazard Ratio

UKPDS

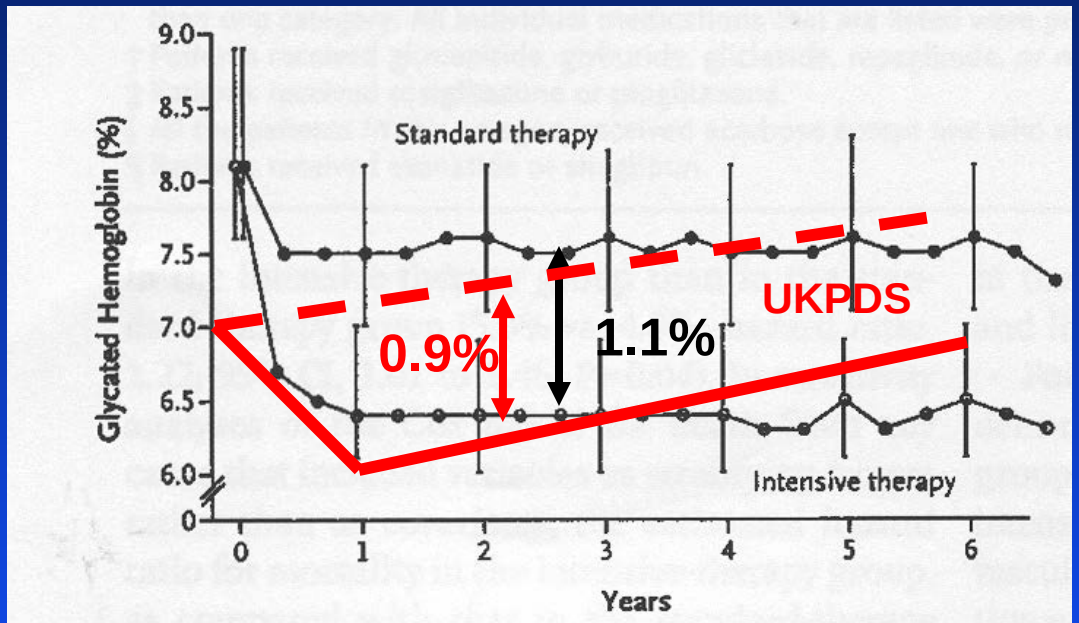
Intensive (SU/Ins) *vs.* Conventional glucose control



NEJM 2008; 359:

ACCORD Study

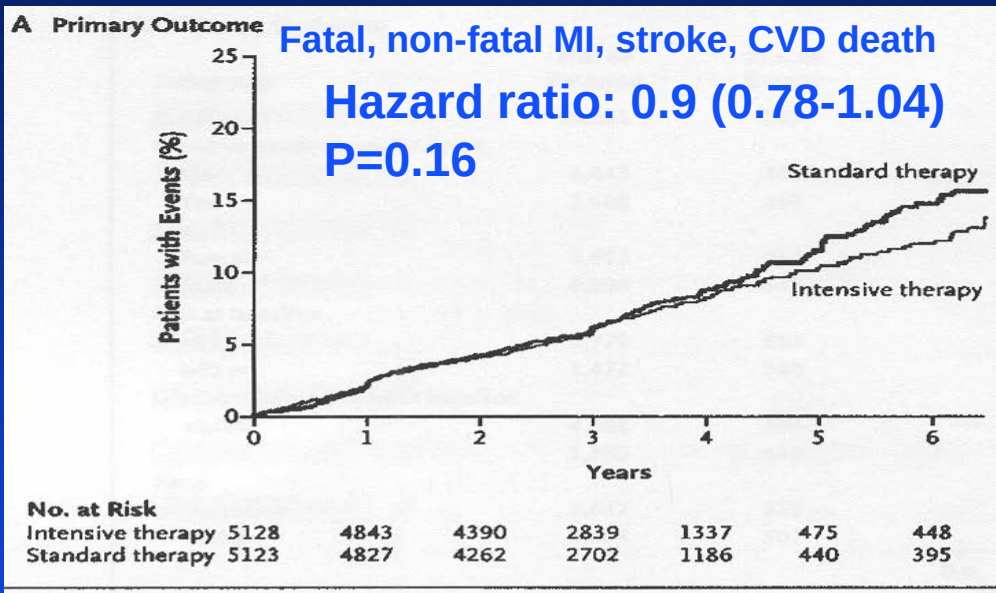
Action to Control Cardiovascular Risk in Diabetes Study



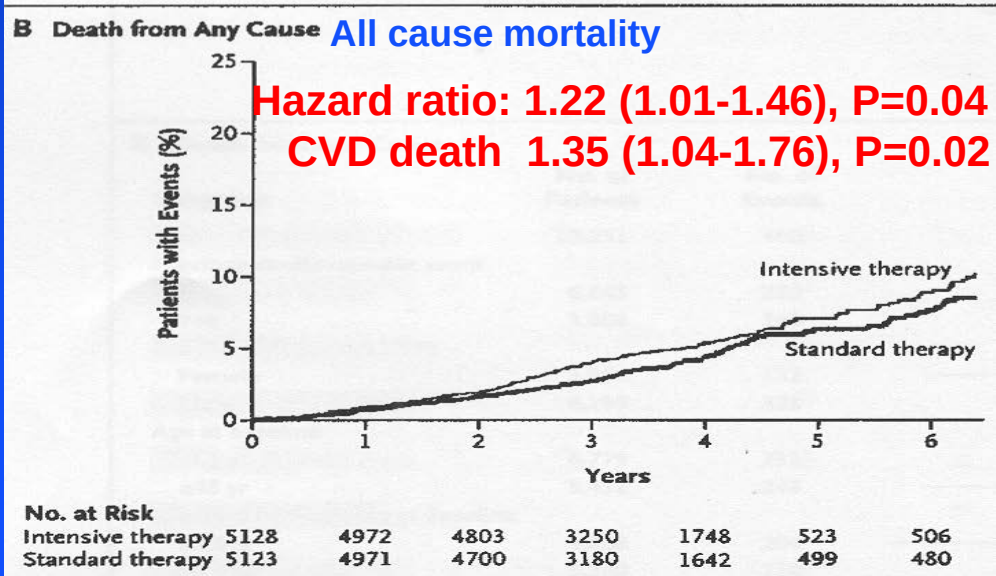
No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.
I bars denote interquartile ranges.

N Engl J Med 2008;358:2545



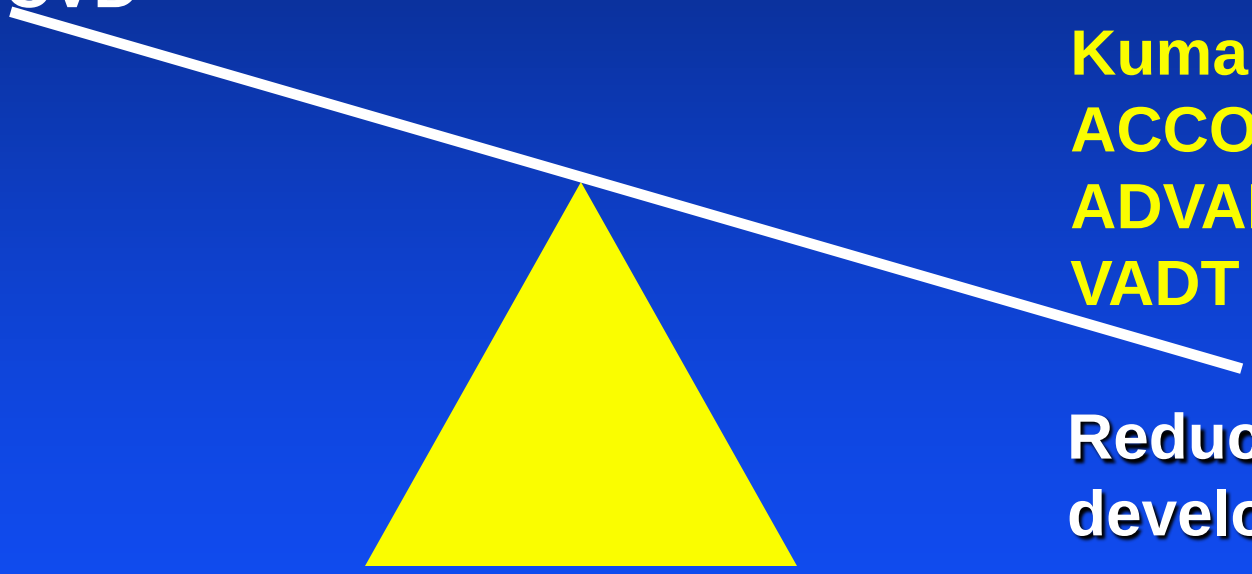
No. at Risk							
Intensive therapy	5128	4843	4390	2839	1337	475	448
Standard therapy	5123	4827	4262	2702	1186	440	395



No. at Risk							
Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

Intensive Therapy of Type 2 Diabetes

Minimal hypoglycemia
Weight gain
No excess CVD
Effort
Expense



UKPDS
Kumamoto
ACCORD
ADVANCE
VADT

Reduced development and progression of microvascular complications

Development of Medications Used in the Treatment of Type 2 Diabetes

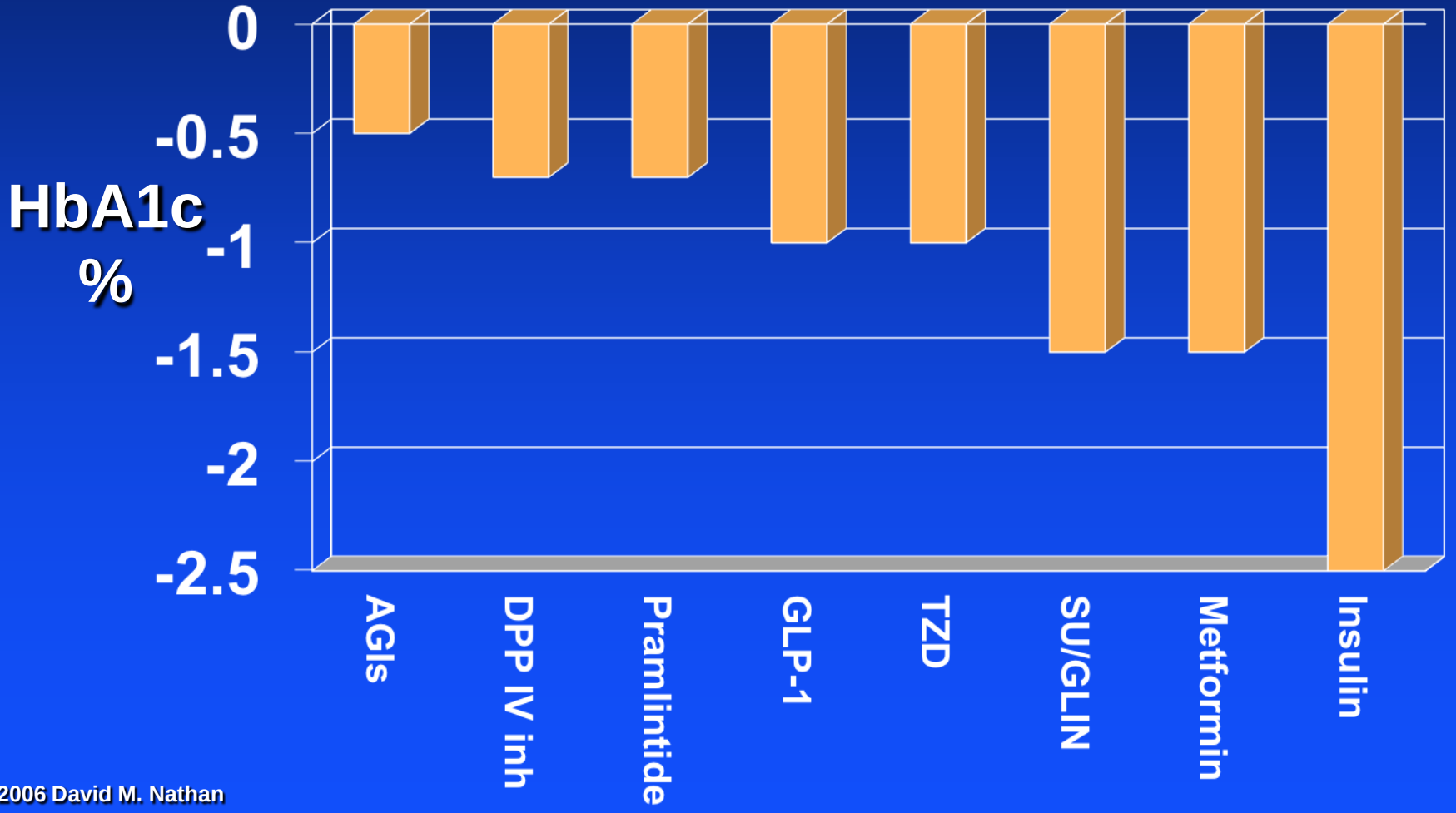
Major Premises

Selection of Interventions

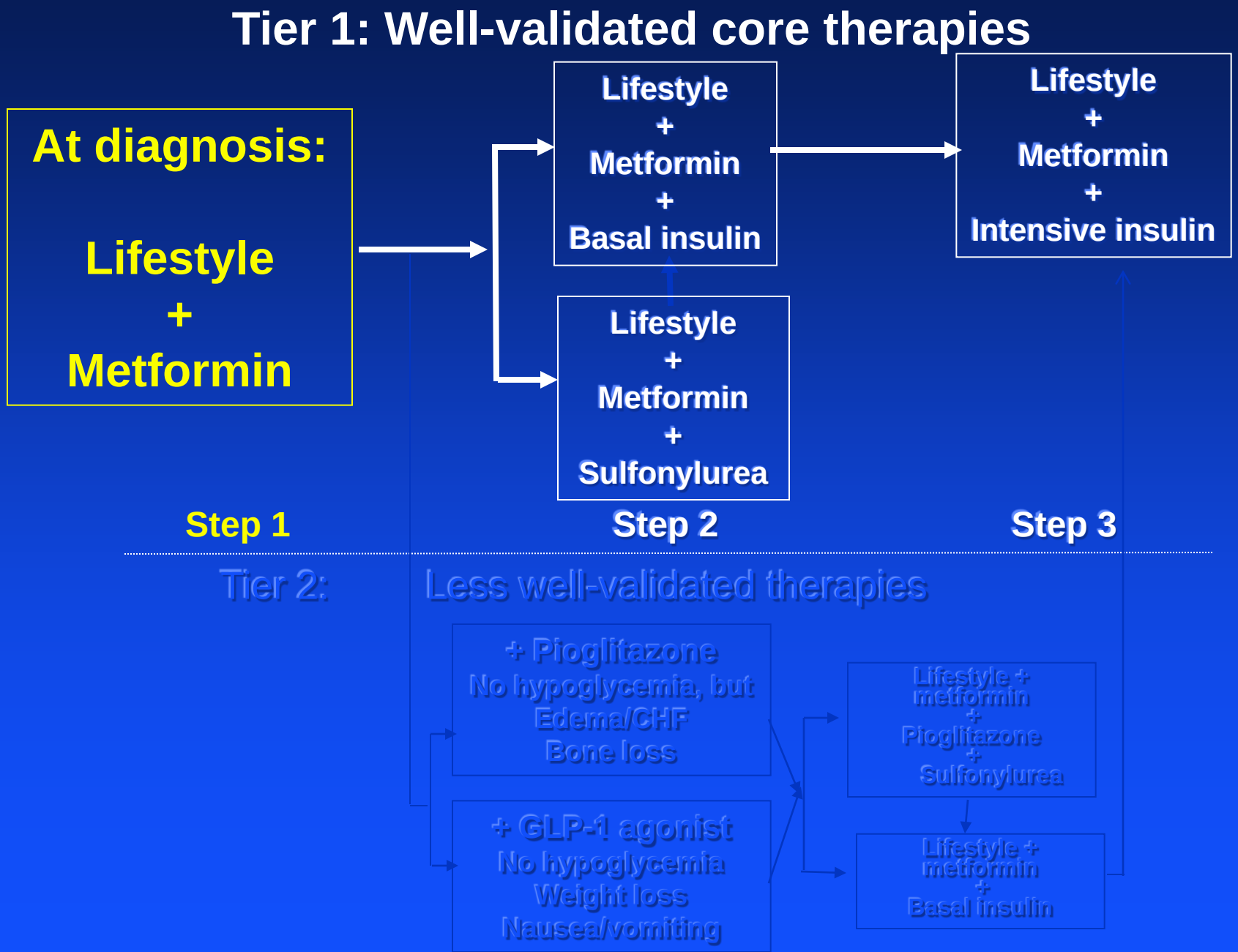
- Effectiveness in lowering A1c
  - Use more effective drugs if initial A1c higher
  - Can use less effective medications if A1c < 8.5
- Safety
- Side-effects, tolerability/acceptance
- Other characteristics, effect (s) on
  - Weight
  - CVD risk factors
  - Beta-cell preservation
- Cost

Relative Merits of Hypoglycemic Agents

Decrease in HbA1c: Potency of Monotherapy



Consensus algorithm-2009



First Step- Metformin + Lifestyle

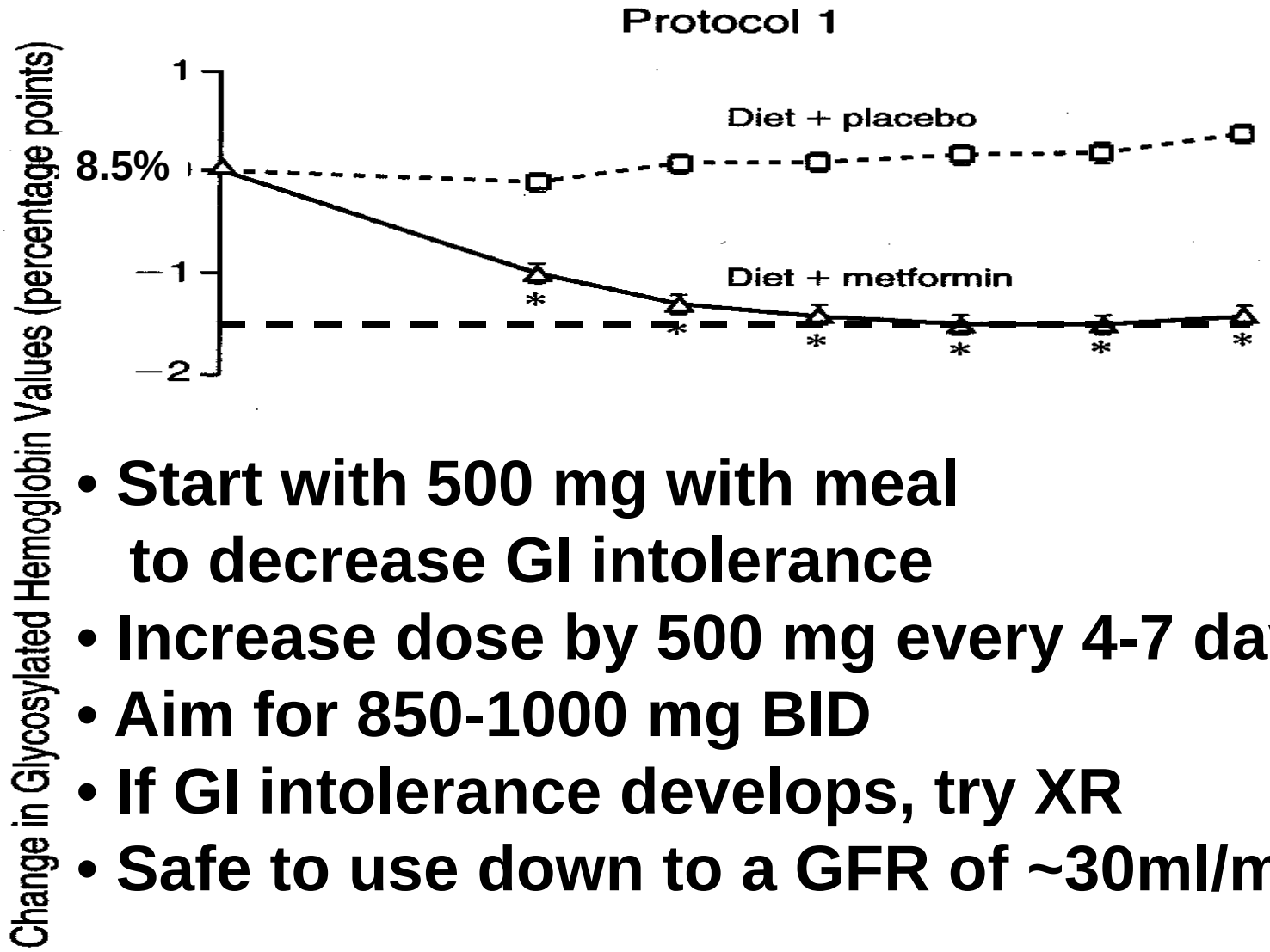
- Recognizes failure of life-style alone
- Inhibits hepatic glucose output- predominantly lowers fasting glycemia
- Cellular mechanism unknown (AMP kinase)
- Lowers HbA1c by ~1.5%
- Effective in obese and non-obese patients and in preventing diabetes in pre-diabetics (DPP)
- Glucophage off-patent, very inexpensive

Intensive Therapy of Type 2 Diabetes

Lifestyle: Diet and Exercise

- Highly effective in short term
- 5-10 lb weight loss usually sufficient to ameliorate hyperglycemia
- Long-term benefit parallels results of obesity therapy

Metformin



- **Start with 500 mg with meal to decrease GI intolerance**
- **Increase dose by 500 mg every 4-7 days**
- **Aim for 850-1000 mg BID**
- **If GI intolerance develops, try XR**
- **Safe to use down to a GFR of ~30ml/min**

DeFronzo NEJM 1995;333:541

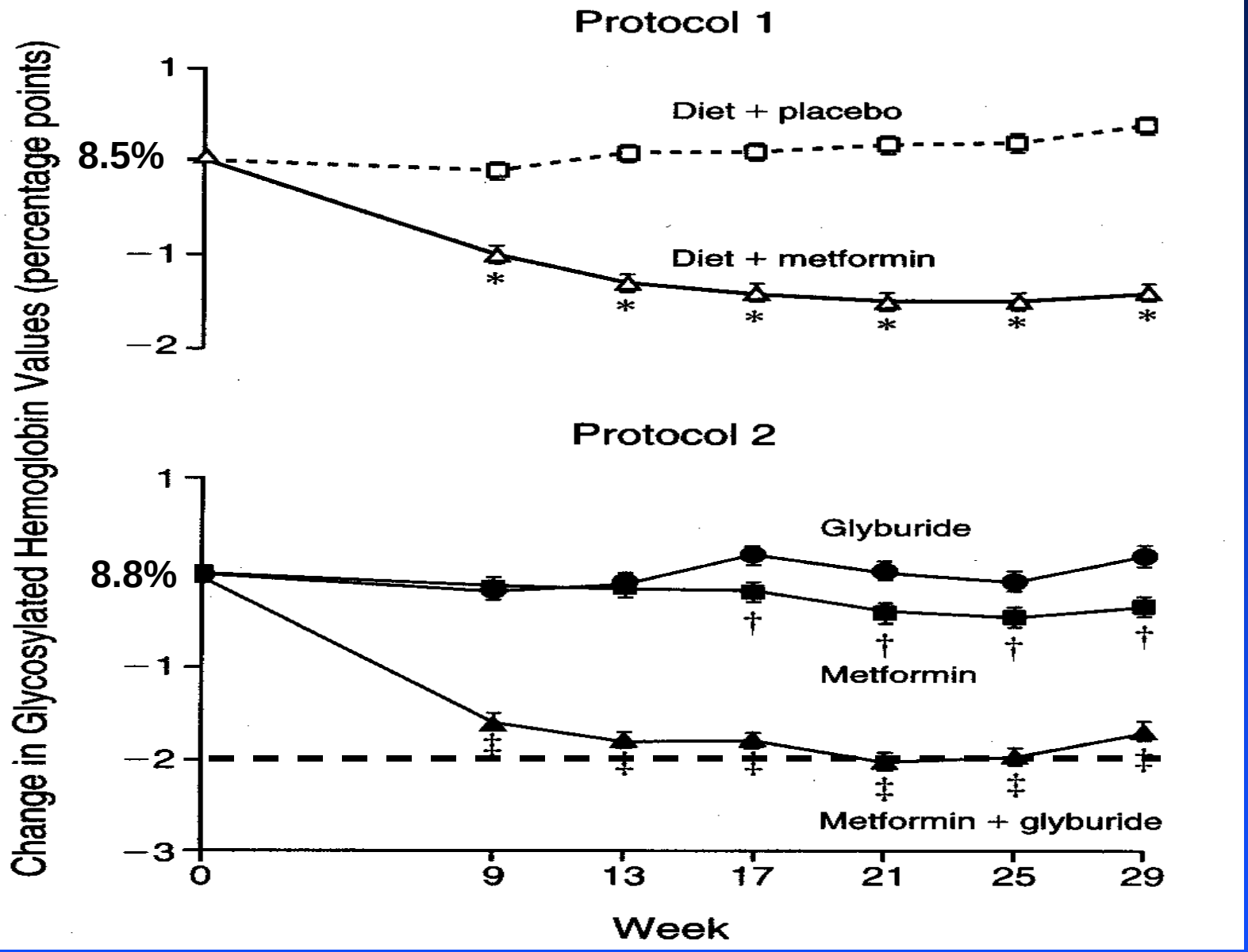
Step Two

Adding to Lifestyle and Metformin

If HbA1c $\geq$ 7%

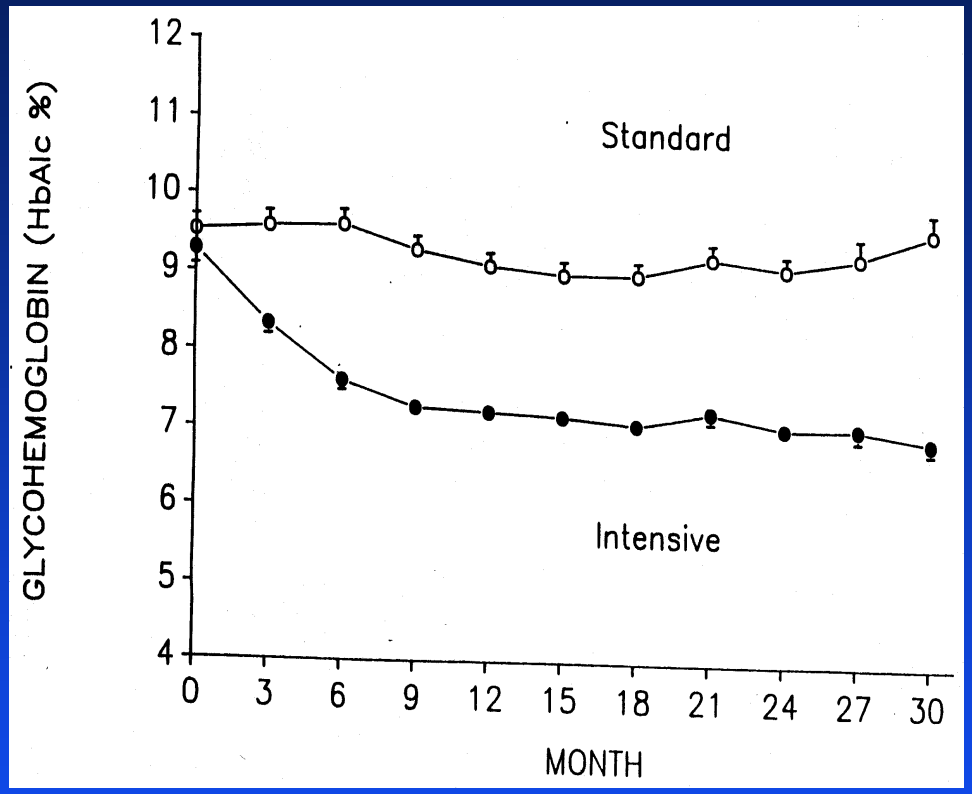
Add either sulfonylurea
or
Basal Insulin

Metformin + Sulfonylurea

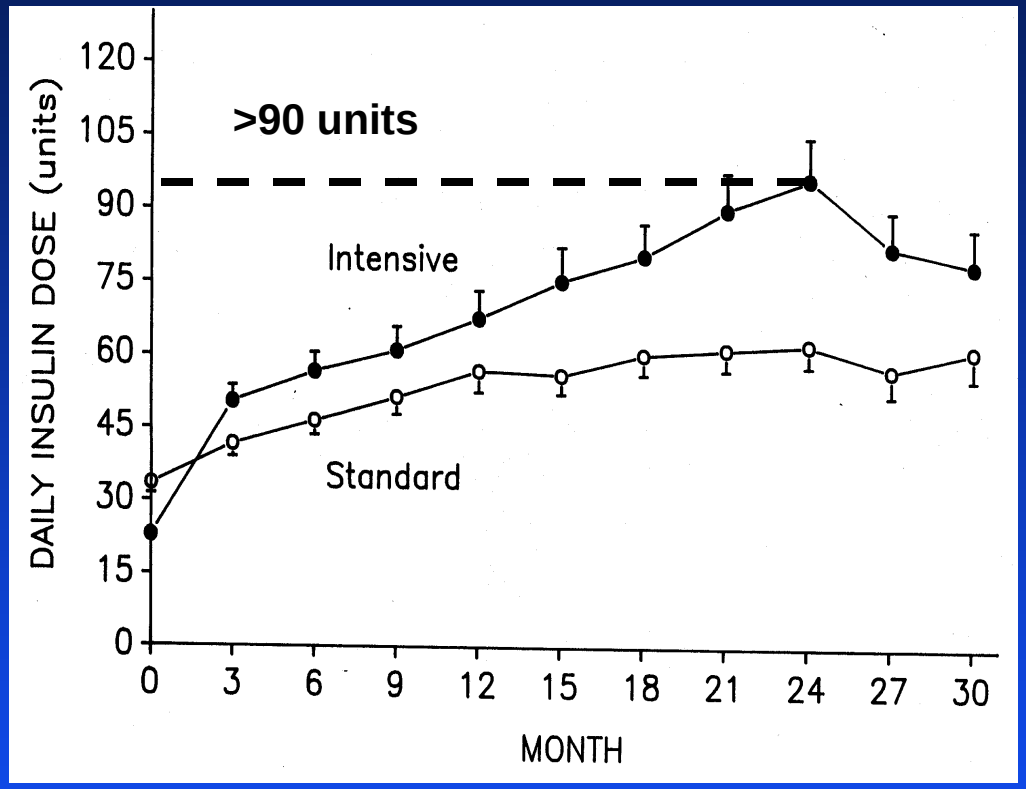


DeFronzo
NEJM
1995;333:541

Insulin Therapy



HbA1c



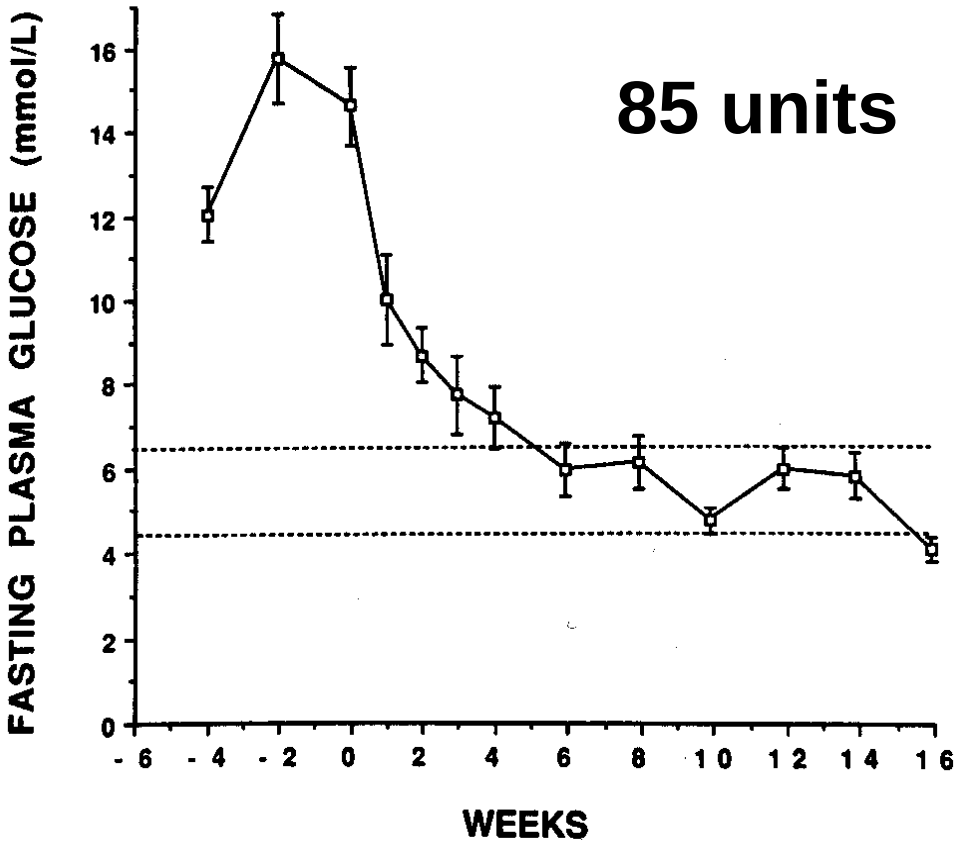
Insulin dose

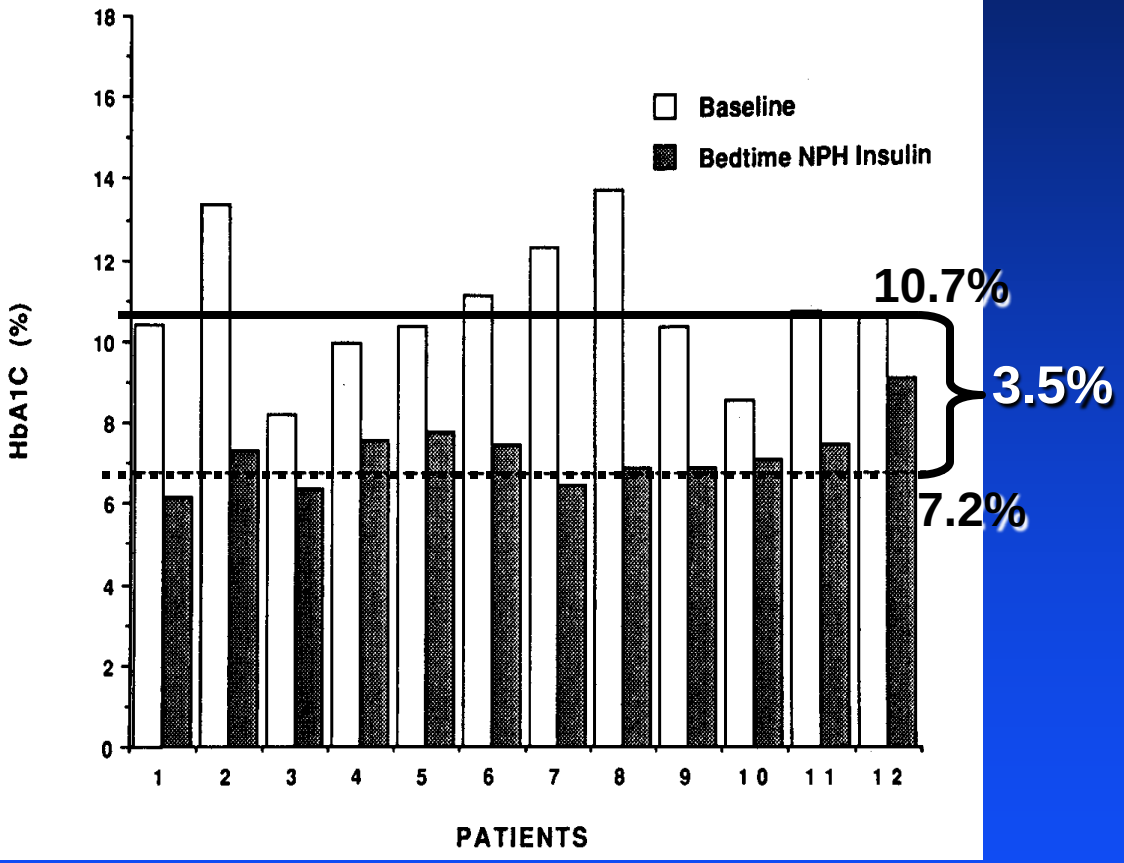
153 Type 2 diabetic men
Mean age 60

VA Cooperative Study
Diabetes Care 1995;18:1113

Insulin Therapy of Type 2 DM

Bedtime NPH

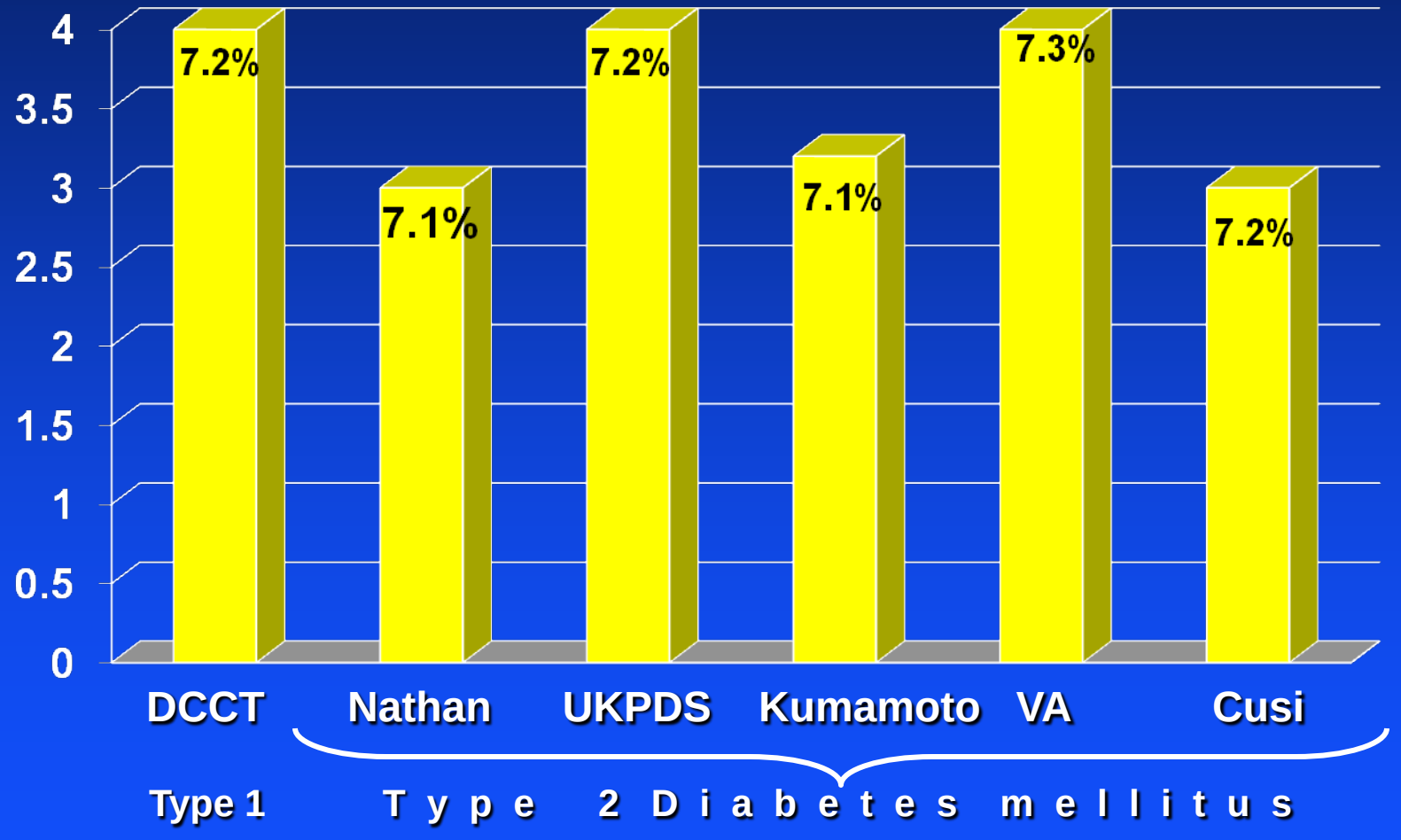




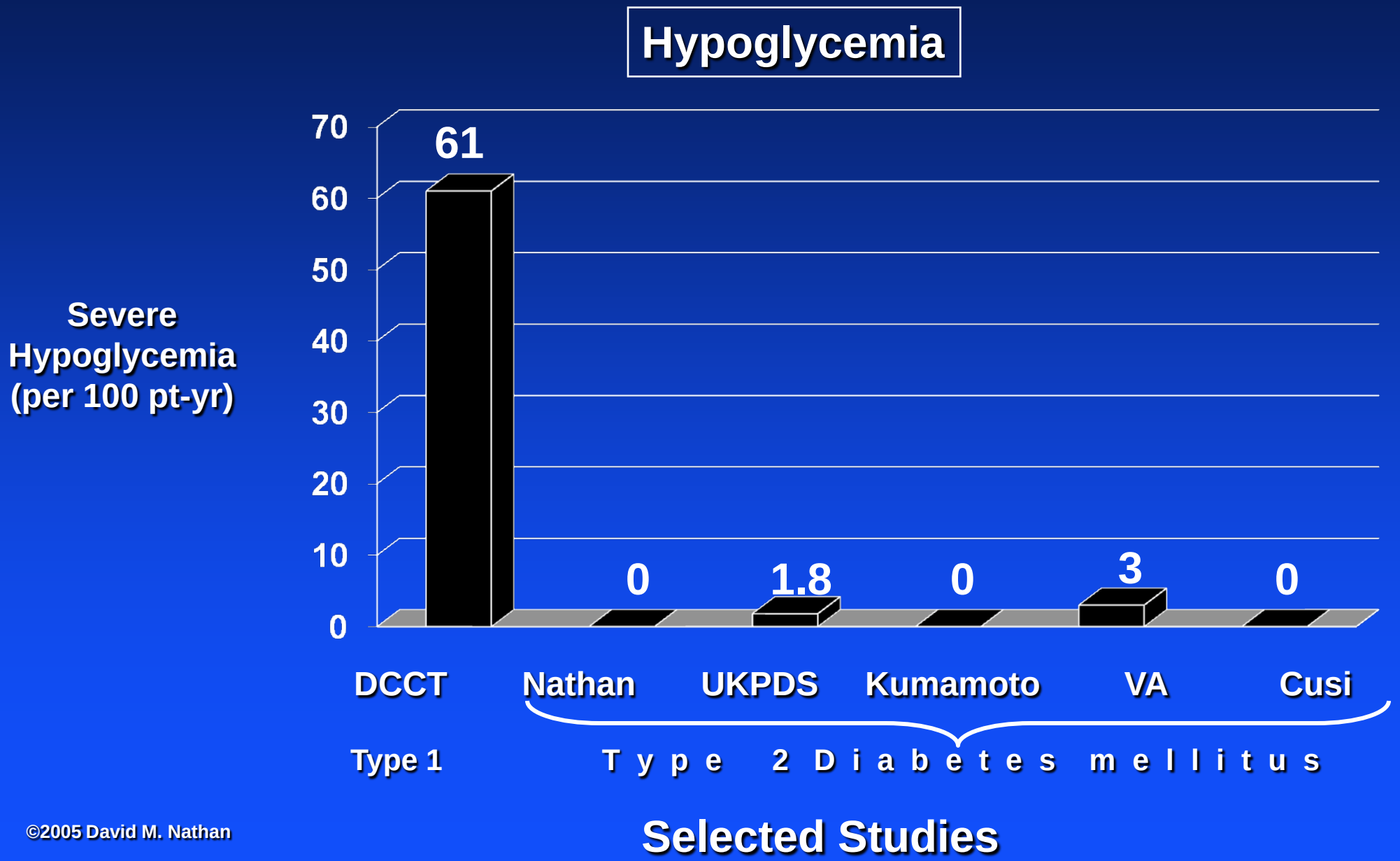
Cusi et al. Diabetes Care 1995;18: 843

Results of Insulin Monotherapy

Glycemia

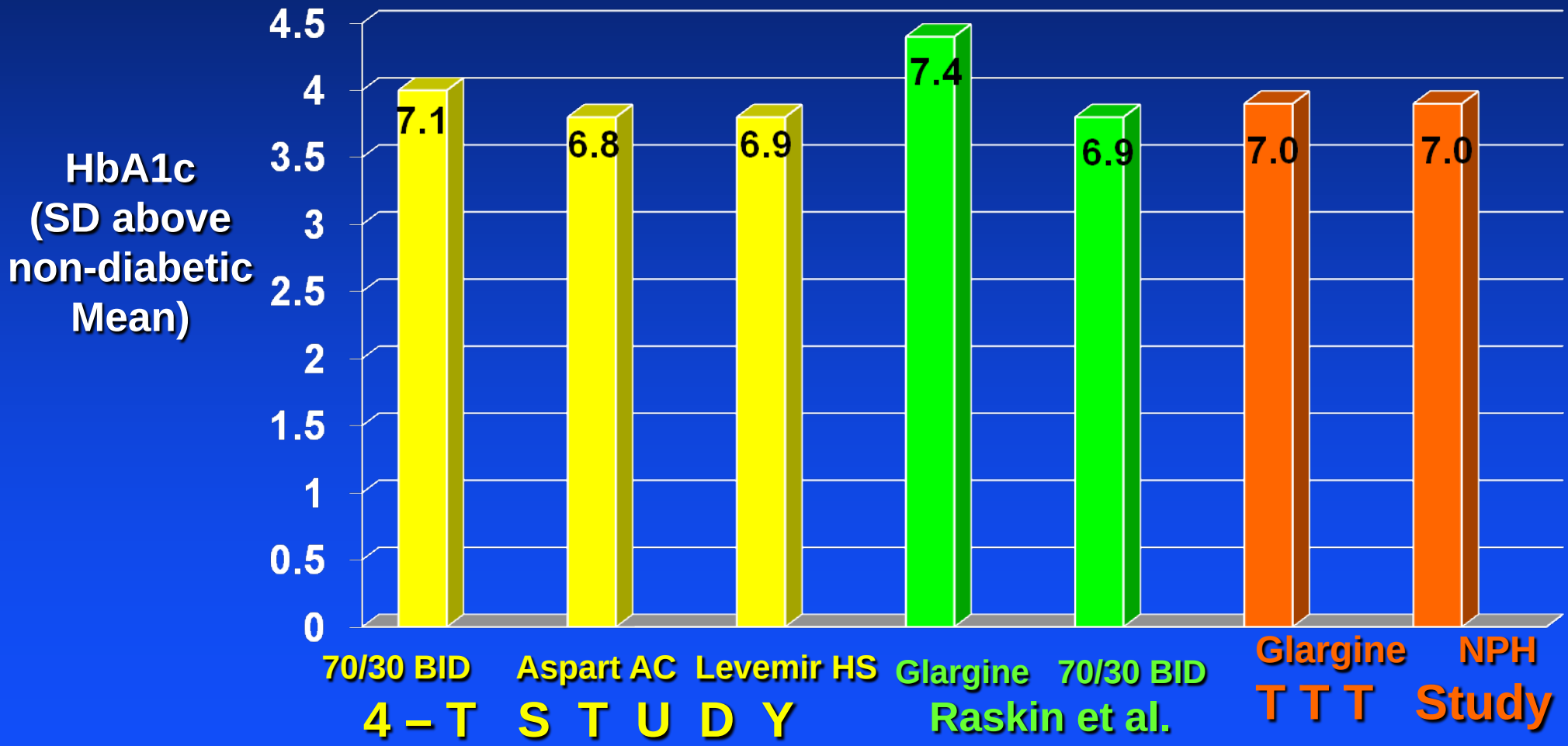


Results of Insulin Monotherapy

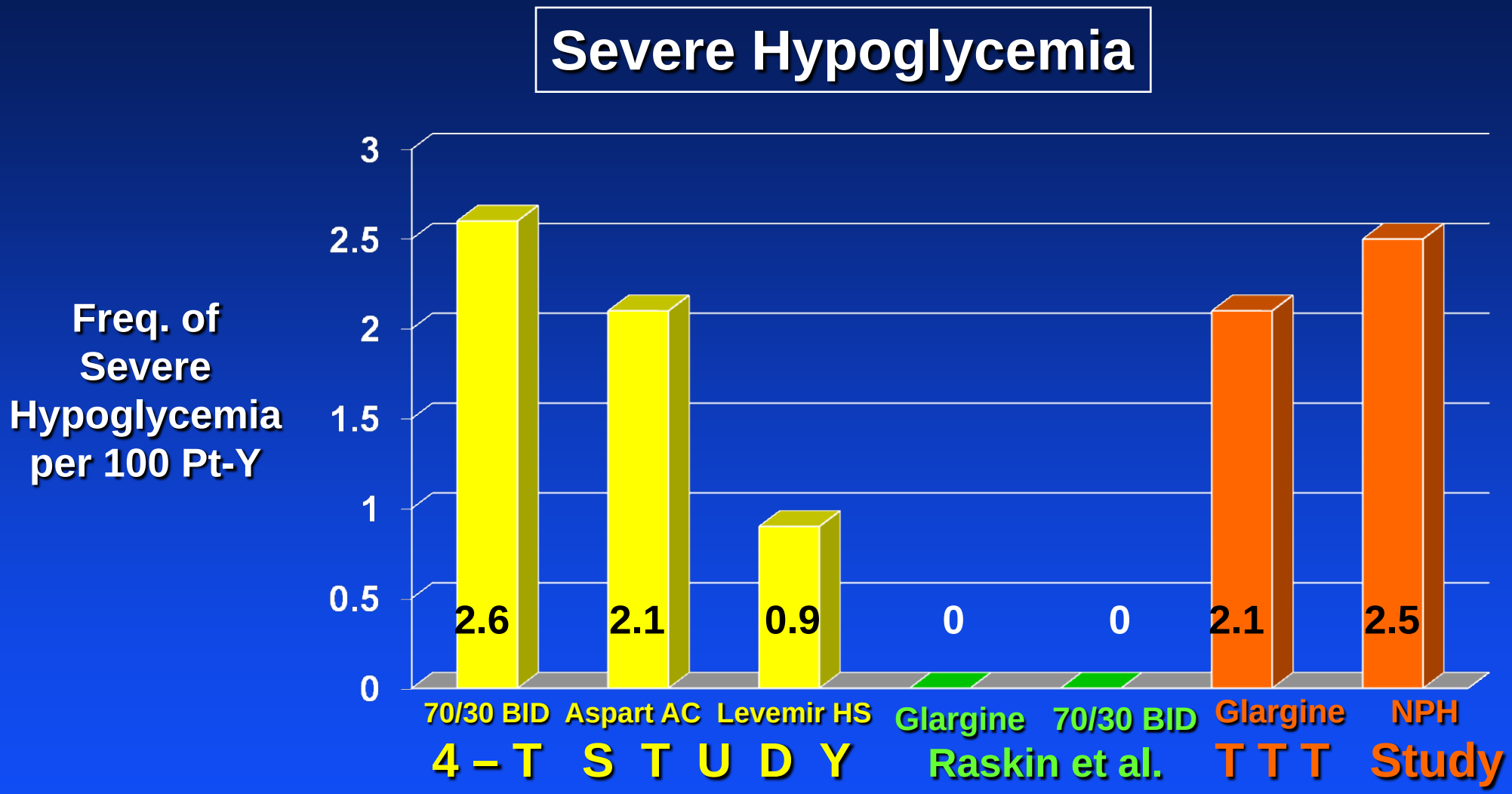


Results of Insulin Therapy with Metformin

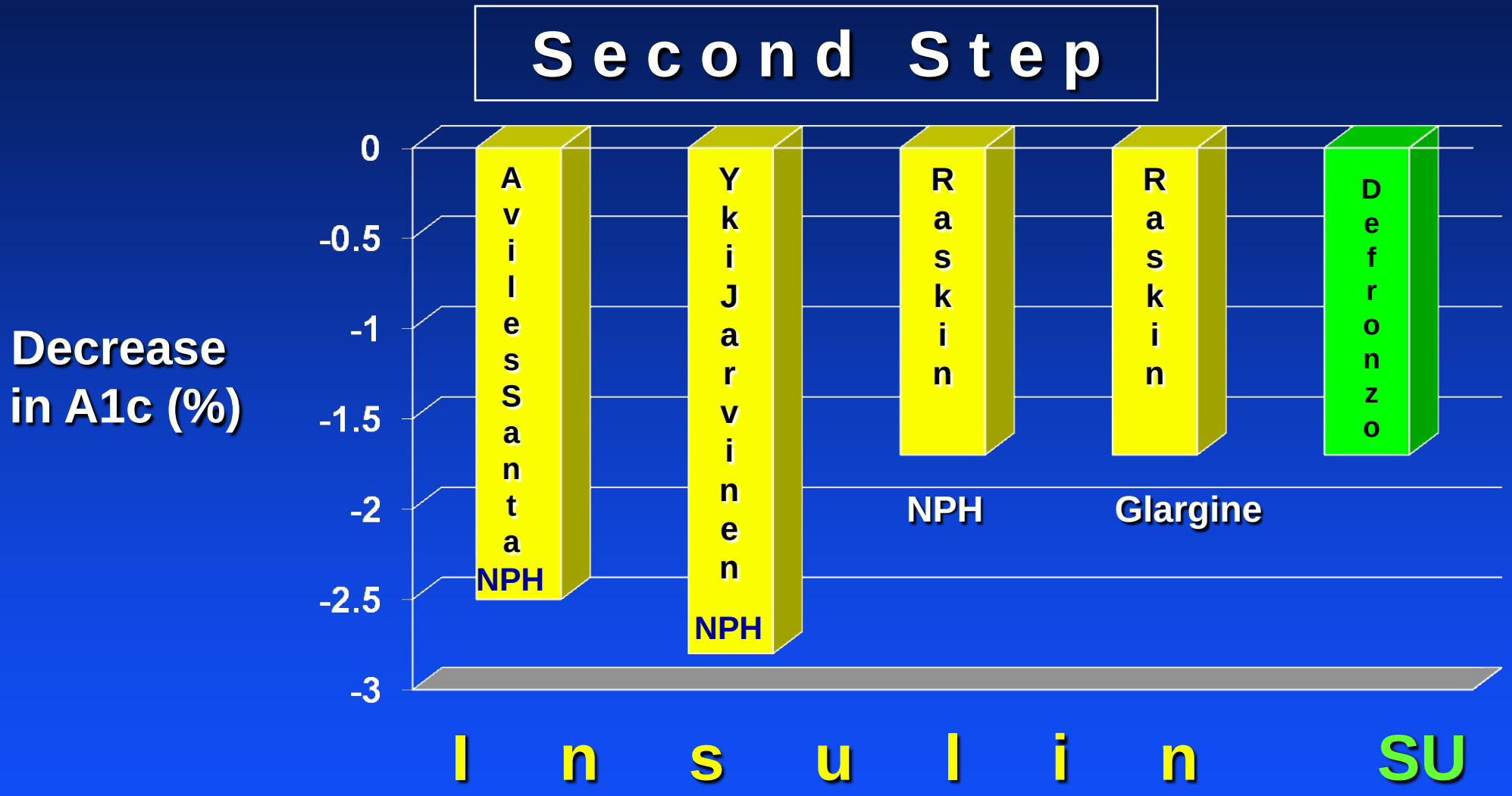
Combination Therapy: Glycemia



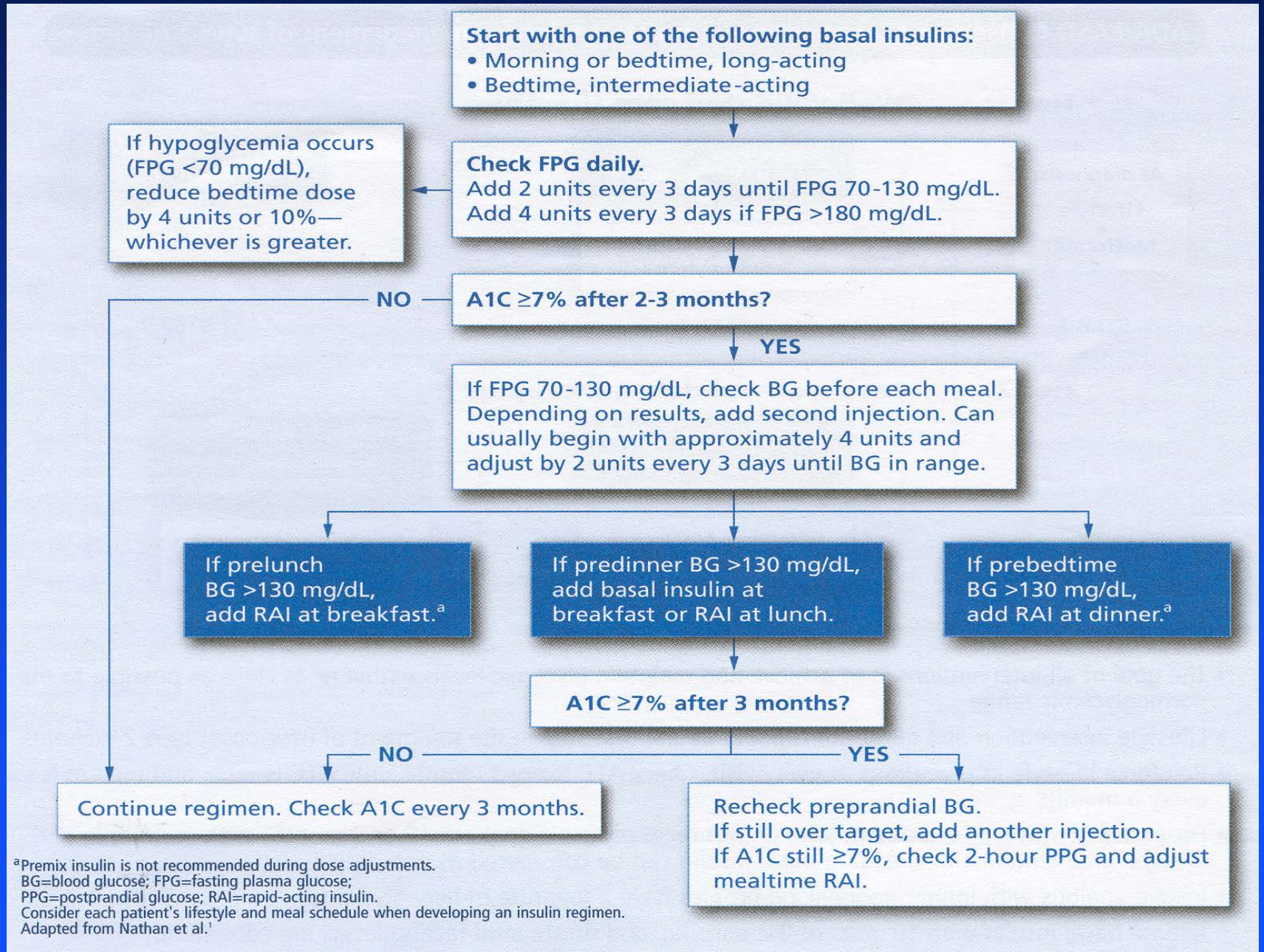
Results of Insulin Therapy with Metformin



Results of Metformin Plus Other Therapy



Consensus algorithm: Initiation and adjustment of insulin



[a]Premix insulin is not recommended during dose adjustments.
BG=blood glucose; FPG=fasting plasma glucose;
PPG=postprandial glucose; RAI=rapid-acting insulin.
Consider each patient's lifestyle and meal schedule when developing an insulin regimen.
Adapted from Nathan et al.[1]

Diabetologia 2009; 52:17-30
Diabetes Care 2009;32:193-203

Choice of Insulin

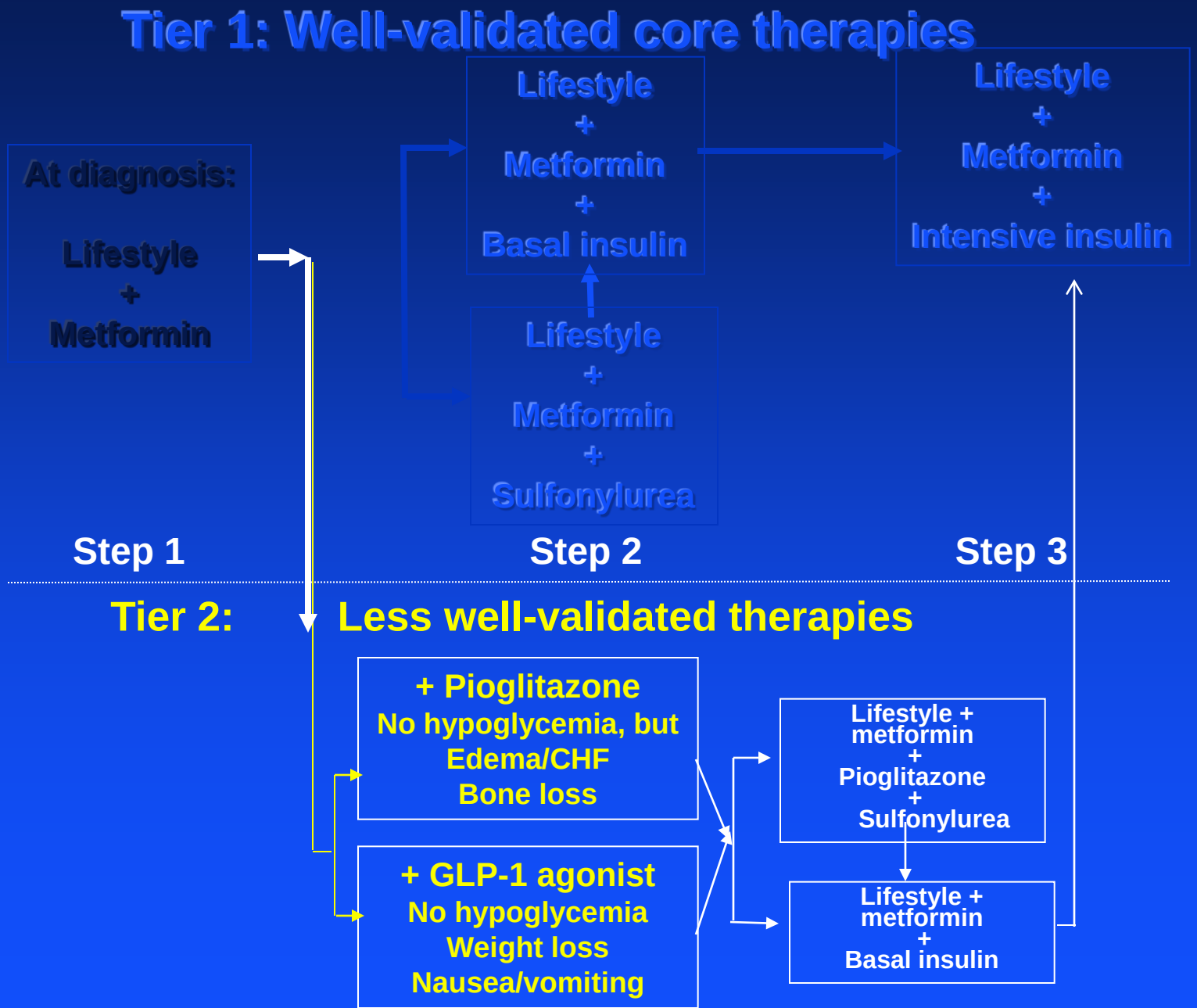
4-T Study: 3 year results

Initial randomized therapy	HbA1c/% <7 (%)	Weight gain (kg)	Dose (Units/day)	% on two insulin types	Hypoglycemia Severe (%)
70/30	7.1/51	5.7	70	67	2.6
AC aspart	6.8/67*	6.4	86	74	2.1
Basal	6.9/64*	3.6*	88*	82*	0.9*

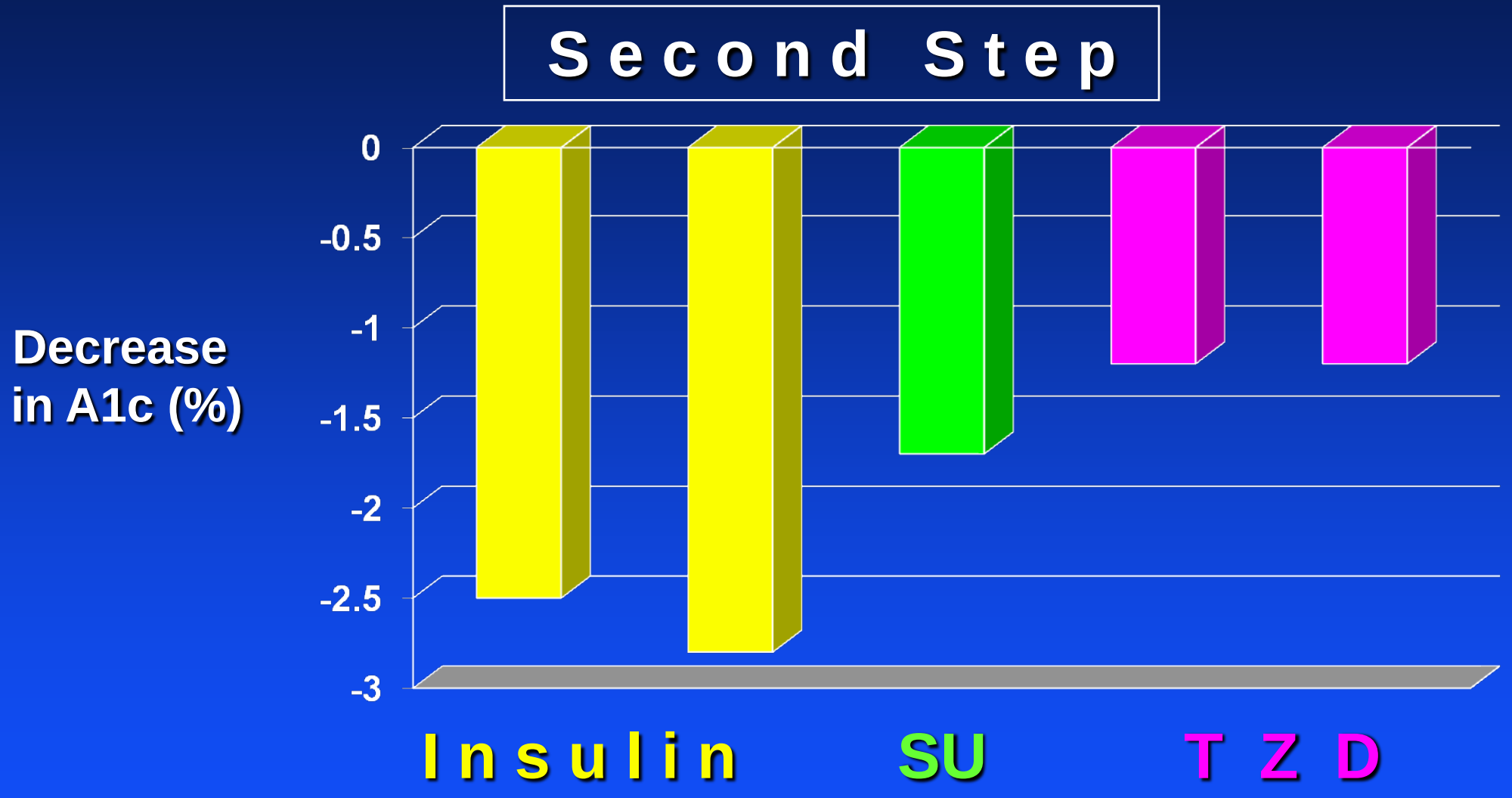
- Similar median A1c results, although more patients on initial basal insulin achieved < 7% goal
- Most patients need more than 1 type of insulin over 3 yr
- Less weight gain and hypoglycemia with initial basal

Holman NEJM 2009;361:1736

Consensus algorithm-2009



Results of Metformin Plus Other Therapy



Intensive Therapy of Type 2 diabetes

Thiazolidinediones

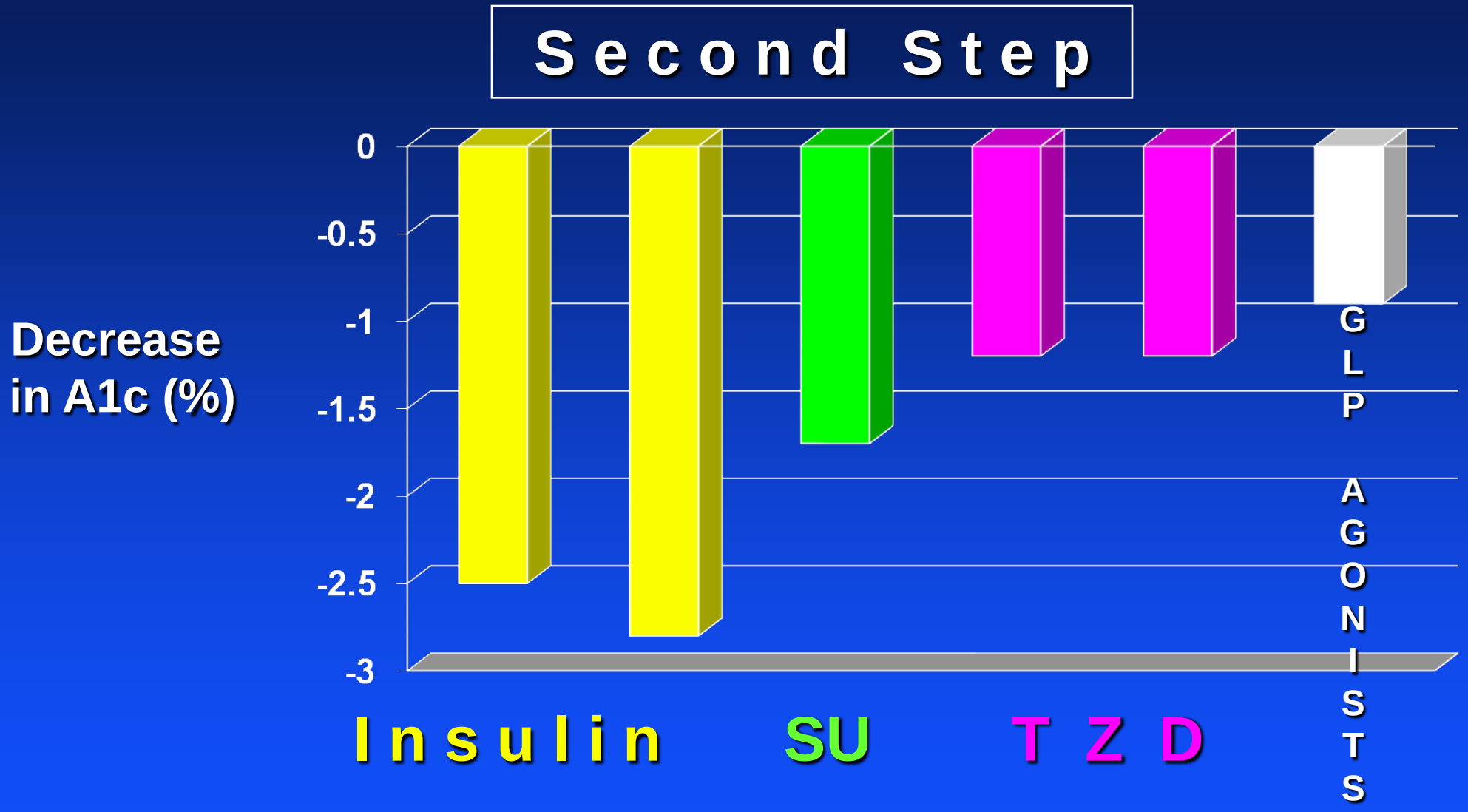
- Relatively weak as monotherapy
- More potent in combination with insulin, metformin, or sulfonylurea/glitinide
- Generally well tolerated- edema, CHF, bone loss
- Liver function monitoring no longer obligatory
- Rosiglitazone and pioglitazone available
- Pioglitazone has better lipid effects, ?bladder cancer
- Concern regarding CVD with rosi. - meta-analysis
- No long-term, reliable data

New Drugs

GLP-Agonists:Exenatide

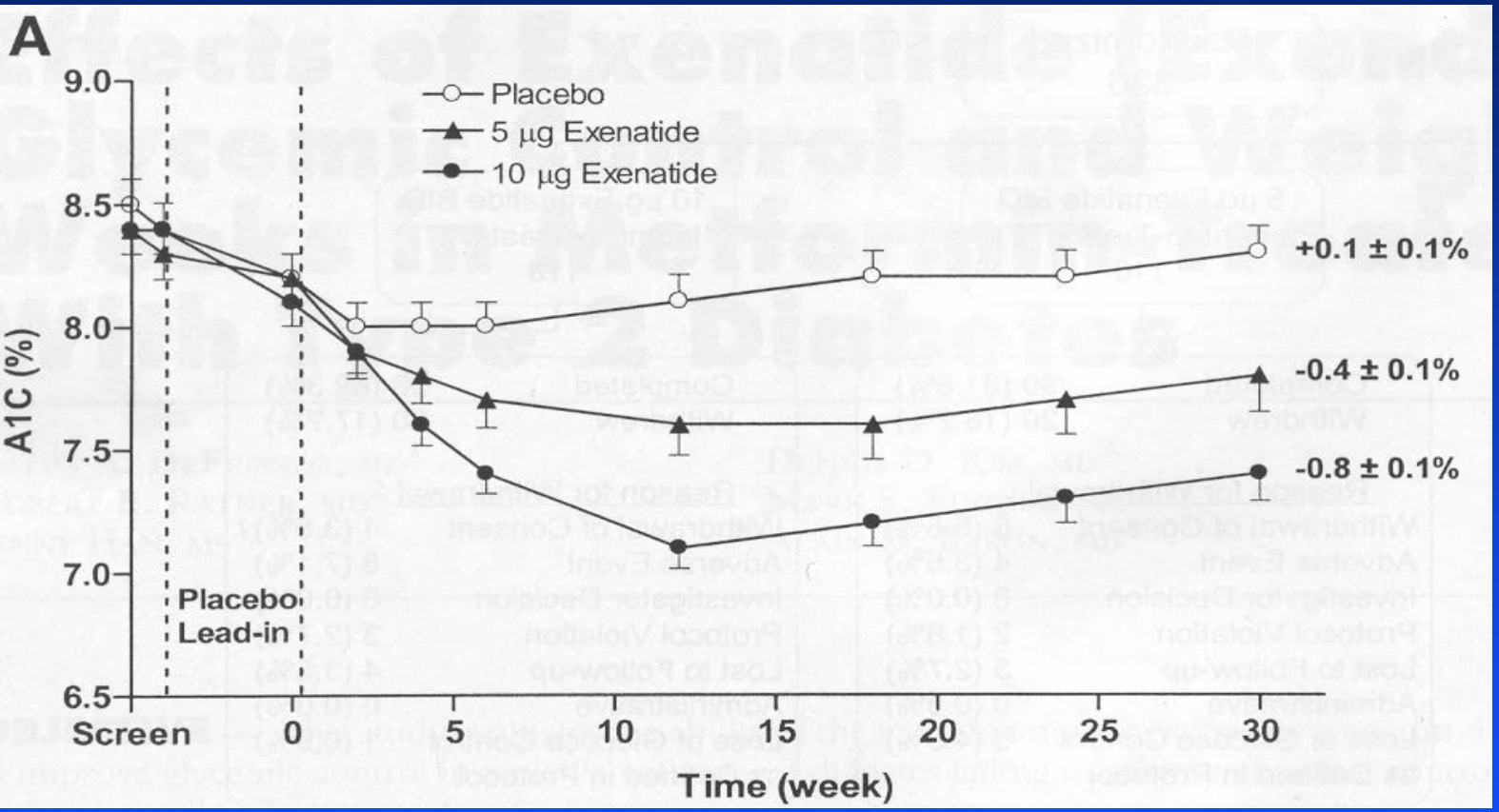
- Exenatide- 39 amino acid
- GLP homologue derived from venom of the Gila lizard “monster” (*Heloderma suspectum*)
- Similar to GLP 1, 7-37
  - Stimulates insulin secretion
  - Suppresses glucagon
  - Delays gastric emptying
  - May decrease appetite
  - GI side-effects

Results of Metformin Plus Other Therapy



New Drugs

Exenatide



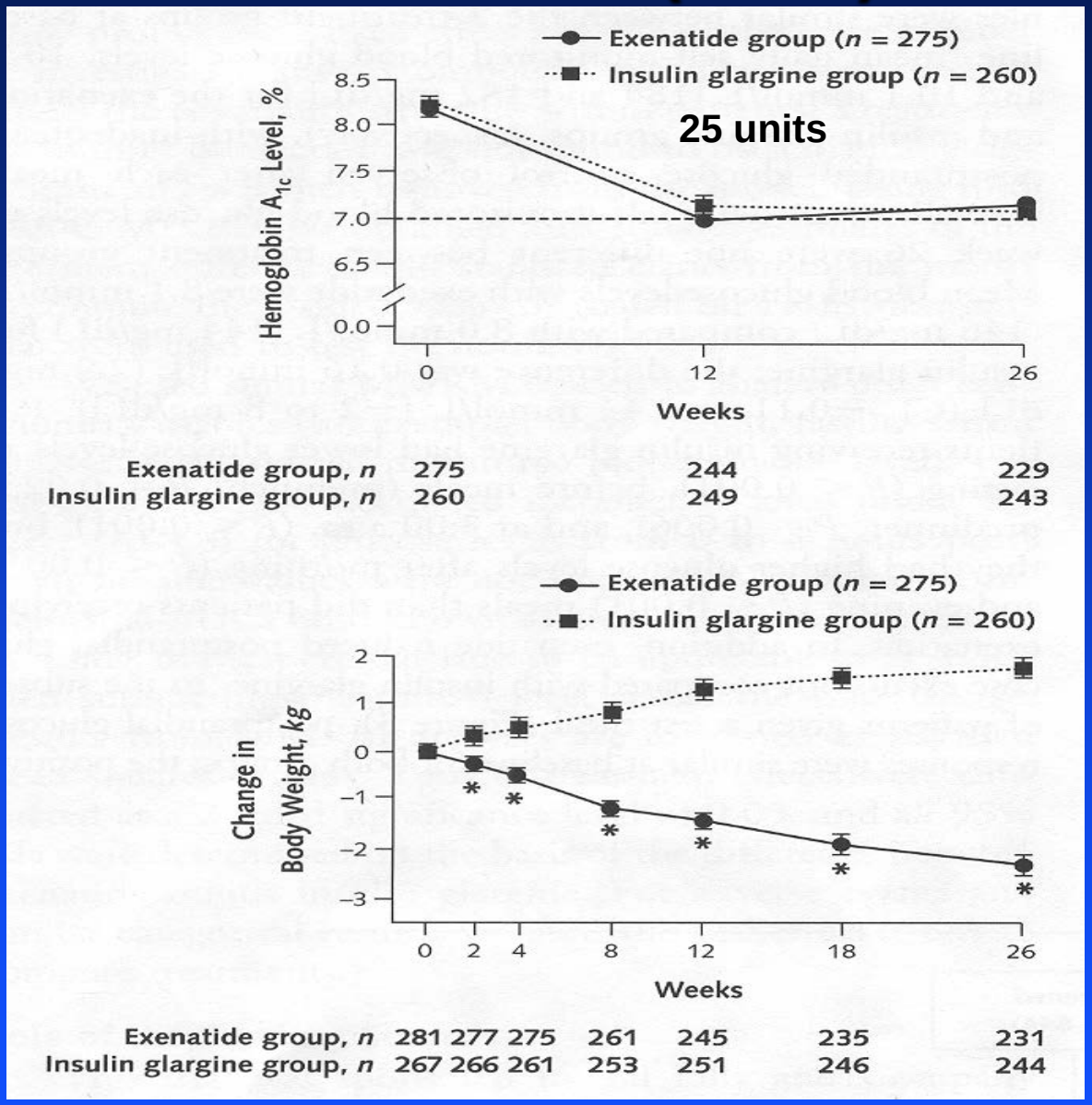
30 week CCT
in metformin
failures (n=336)
19% loss to f/u.
BMI- 34 kg/m^2
HbA1c- 8.2%
Inactive placebo
Injected BID

2.8 kg weight loss with largest dose

12-45% with N/V or diarrhea

DeFronzo et al.
Diabetes Care
2005;28:1092

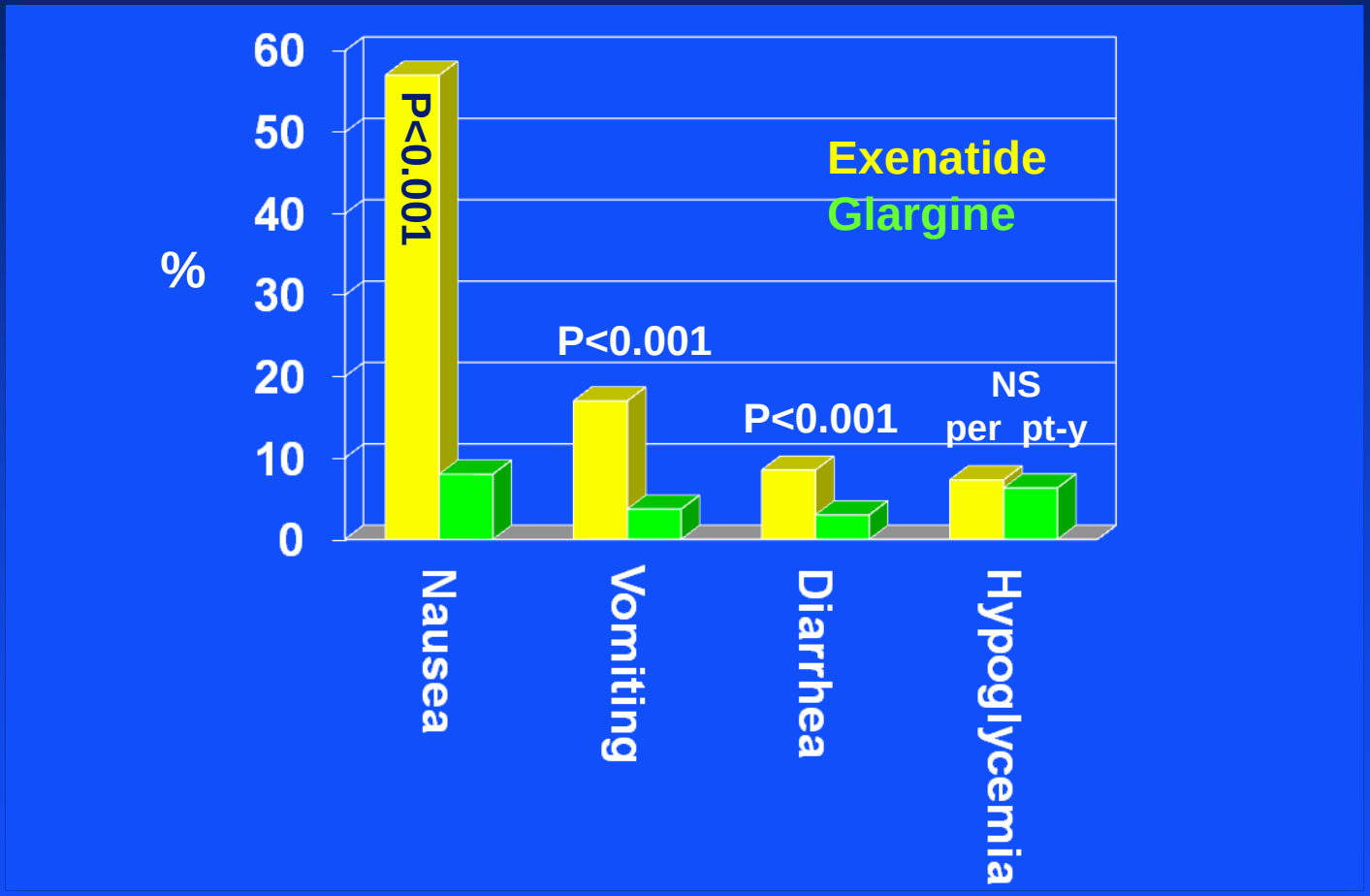
Exenatide (BID) vs Glargine (QD)



- Open label
- Non-inferiority
- Designed by company
- 551 subjects
- 14% loss to followup
- Duration ~ 9.5 y
- Metformin + SU
- A1c 8.3%

Heine et al
Ann Int Med 2005;143:559

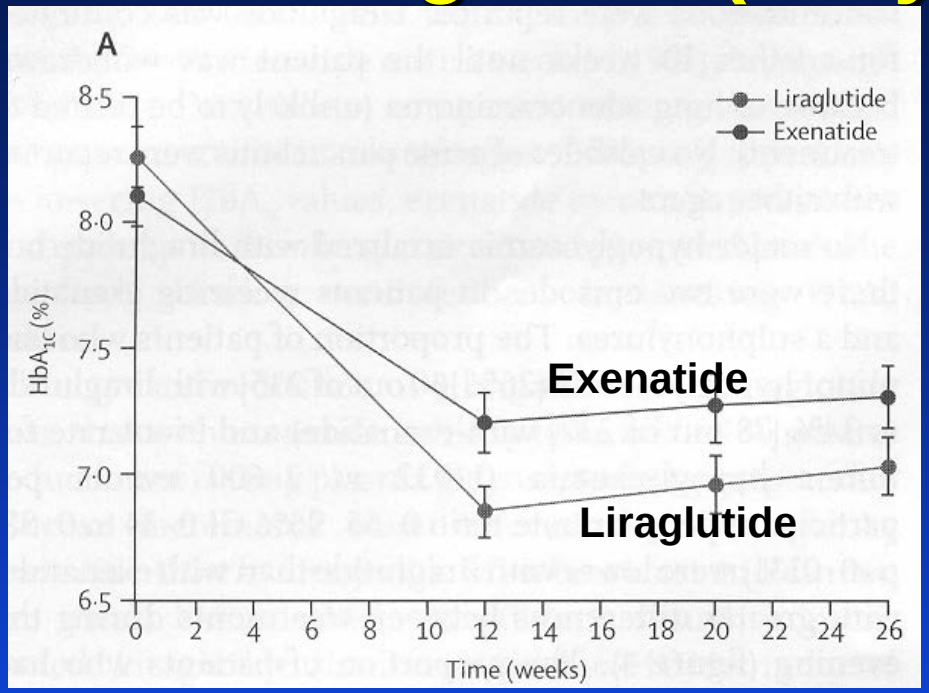
Exenatide (BID) vs Glargine (QD)

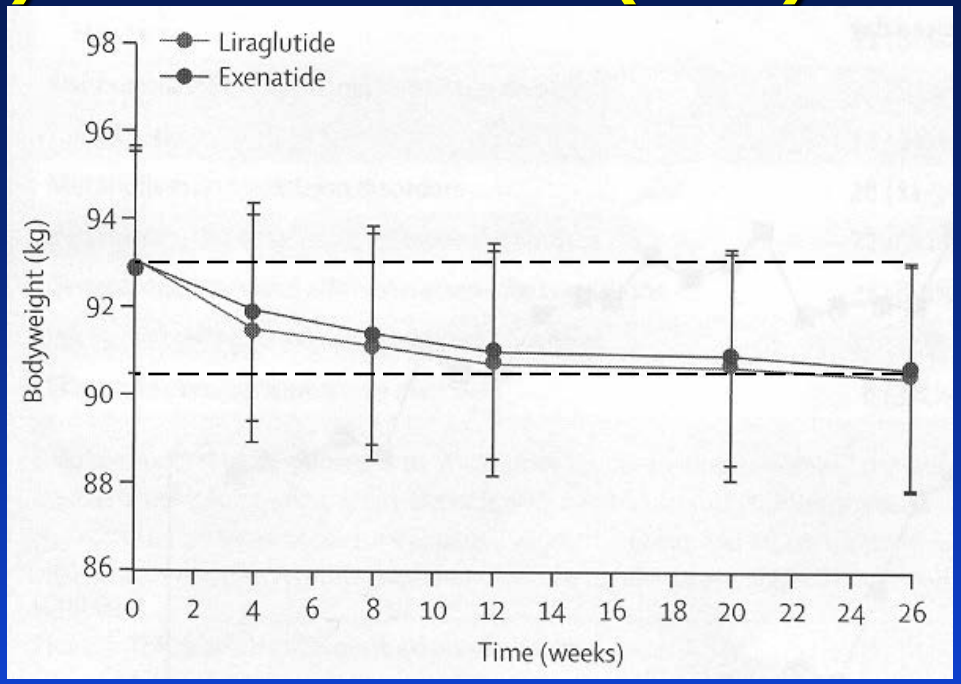


- Open label
- Non-inferiority
- Designed by company
- 551 subjects
- 14% loss to followup
- Duration ~ 9.5 y
- Metformin + SU
- A1c 8.3%

Heine et al
Ann Int Med 2005;143:559

Liraglutide (daily) vs Exenatide (BID)





Open-label, non-inferiority
Designed by Company

- **464 subjects**
- **17% lost**
- **Duration ~8 yr**
- **63% MET +SU**
- **27% MET only**
- **10% SU only**
- **A1c- 8.2%**

No differences in
Hypoglycemia
Weight loss
GI side effects

Buse et al
Lancet 2009;374:39

Reasons Newer Medications Not Chosen

- Comparable or lower effectiveness in lowering glycemia than older drugs
  - alpha-glucosidase inhibitors, amylin analogues, DPP 4 inhibitors
- Side-effects
  - αGI- GI
  - GLP analogues- GI
  - Amylin- GI
- Experience- limited for all
- Cost- higher than for generics

GLP and DPP4 Inhibitors

GLP and its Analogues

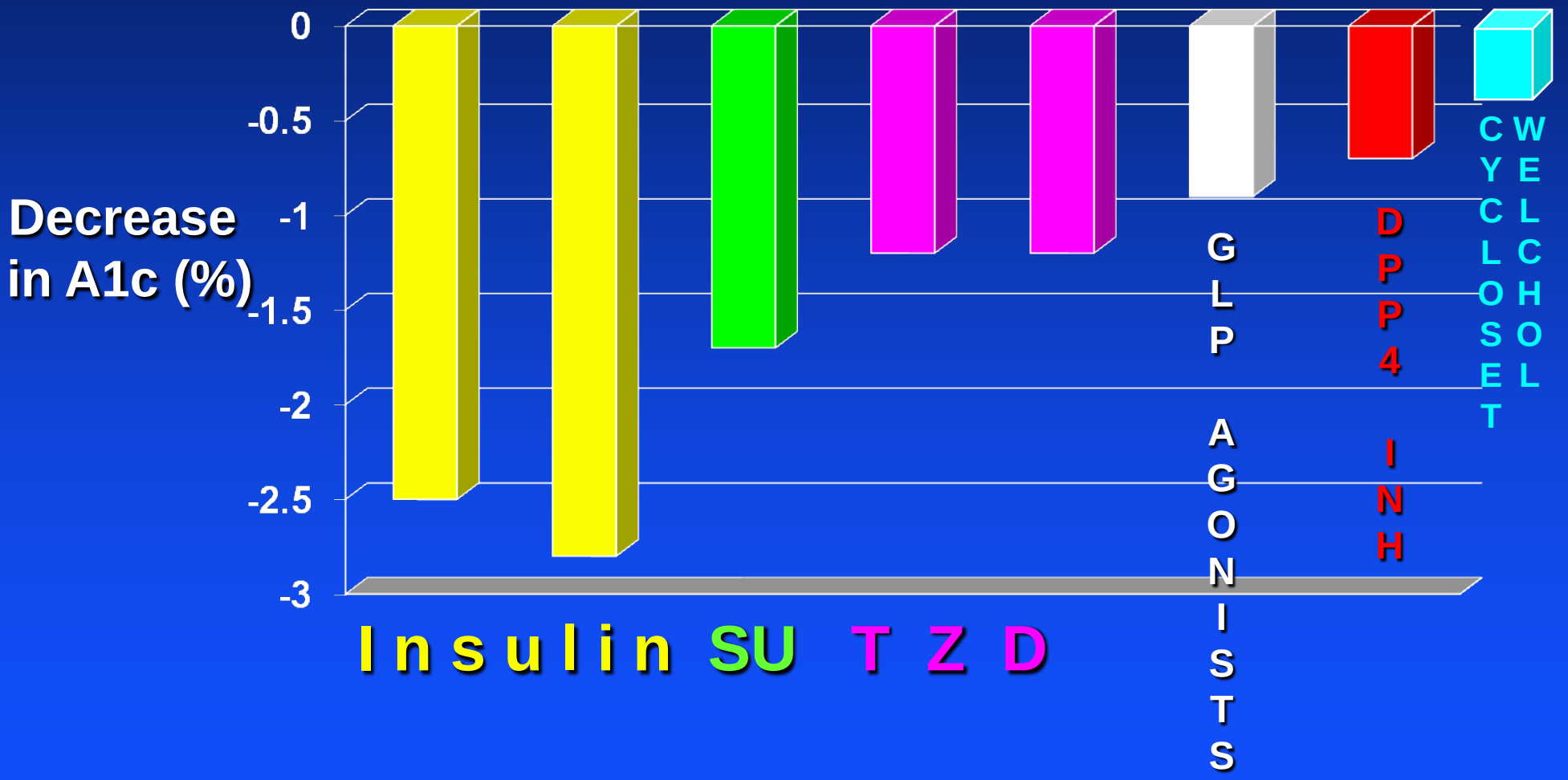
- Stimulate insulin secretion
- Suppress glucagon
- Slow motility
- Lower A1c by ~1.0%
- Injections twice per day
- Weight loss of ~ 5 lb
- Associated with nausea, vomiting, diarrhea in ~40%
- Expensive

DPP 4 Inhibitors

- Inhibit breakdown of endogenous GLP, raising levels by ~2-fold
- Decrease A1c by ~0.6%
- Oral medication
- No weight loss
- No GI side-effects
- Expensive

Results of Metformin Plus Other Therapy

Second Step



If you Use a New Drug

Class	Advantage	Disadvantage	When to Use
DPP-4	Well-tolerated Probably safe One dose	Weak Expensive	Mild DM
GLP-1	Weight loss No hypos	GI side effects Limited efficacy Injections Expensive	Moderate DM Weight gain or risk of hypos major issue
TZDs	No hypos	Edema, CHF, CVD risk, Expensive	Never?

Relative Merits of Hypoglycemic Agents

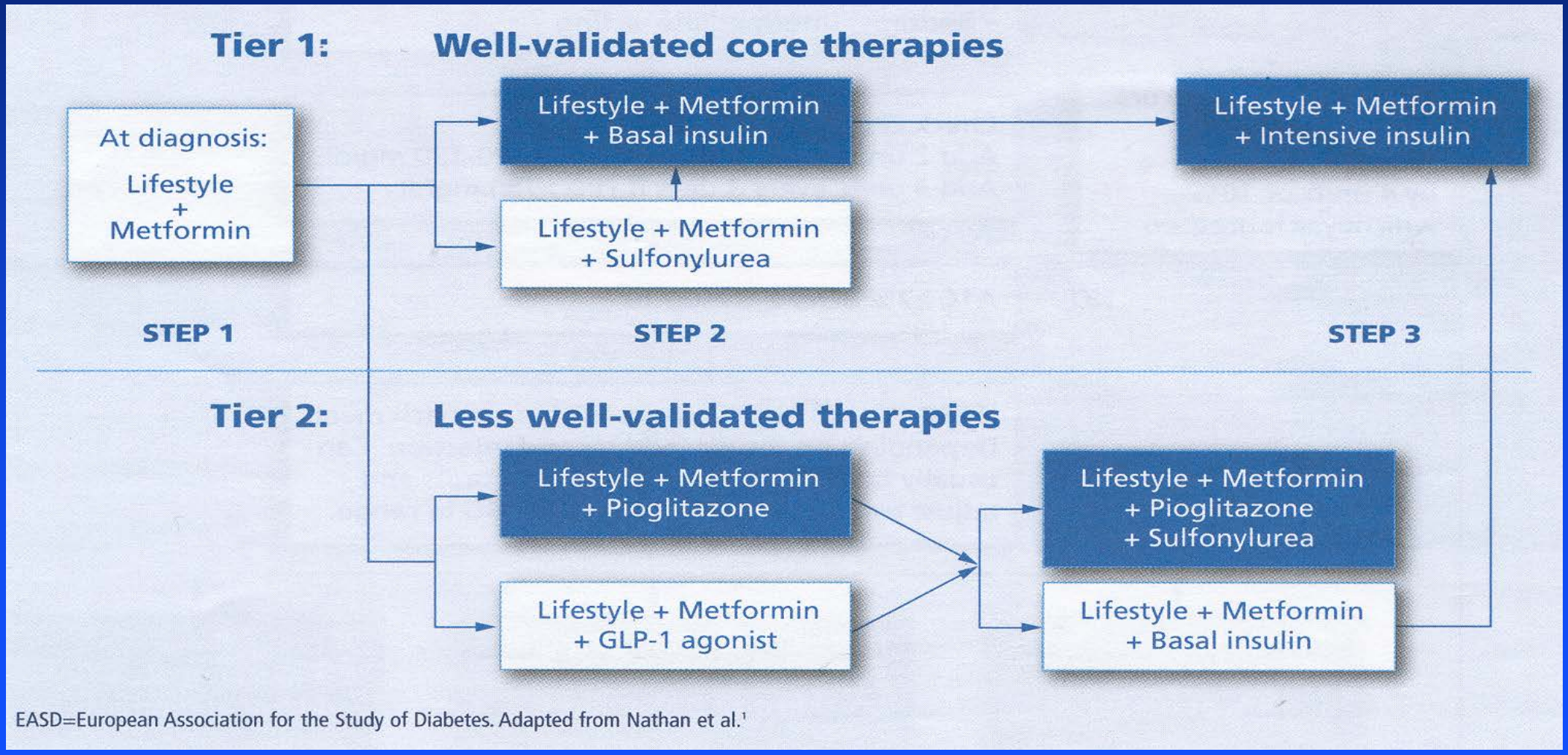
Decrease in HbA1c: Potency of Monotherapy vs Cost

Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

D. M. Nathan · J. B. Buse · M. B. Davidson · E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman

Diabetologia 2009; 52:17-30
Diabetes Care 2009;32:193-203



EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.[1]

Caveats

- Although the algorithm should apply to most people with type 2 diabetes, it does not apply to all
- Individualize therapy
- May select different glycemic goals
  - Elderly
  - Persons with projected life-span too short to benefit
  - Persons where risk for side-effects outweighs benefits
- May select different medications based on
  - Patient acceptance, tolerance
  - Specific risk factors
- Don’t forget other interventions- lipids, blood pressure, CVD prevention